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(54) Title: HETEROAROMATIC CARBOXAMIDE DERIVATIVES FOR THE TREATMENT OF INFLAMMATION

(57) Abstract: The present invention relates to heteroaromatic carboxamide derivatives, compositions comprising such, intermediates, methods of making heteroaromatic carboxamide derivatives, and methods for treating cancer, inflammation, and inflammation-associated disorders, such as arthritis.

HETEROAROMATIC CARBOXAMIDE DERIVATIVES FOR THE TREATMENT OF INFLAMMATION

The present application claims priority under Title 35, United States Code, §119 to United States Provisional application Serial No. 60/340,816 filed October 30, 2001, which is incorporated by reference in its entirety as if written herein.

FIELD OF THE INVENTION

[001] The present invention in general is in the field of anti-inflammatory pharmaceutical agents and specifically relates to heteroaromatic carboxamide derivatives, compositions comprising such, and methods for treating cancer, inflammation, and inflammation-associated disorders, such as arthritis.

BACKGROUND OF THE INVENTION

[002] The following description of the background of the invention is provided to aid in the understanding the invention, but is not admitted to be or describe prior art to the invention.

[003] NF-κB is a ubiquitous transcription factor that plays a prominent role in the activation of the immune system and in stress responses by regulating the transcription of many early, inducible genes including proinflammatory cytokines, adhesion molecules, growth factors, enzymes, and receptors (Ghosh S., May, M. J., and Kopp. E (1998) *Annu. Rev. Immunol.* **16**, 115-260; Zandi, E., and Karin, M. (1999) *Mol. Cell. Biol.* **19**, 4547-4551; Karin, M. (1999) *J. Biol. Chem.* **274**, 27339-27342). Specificity of gene expression is determined at a cellular level by a diverse array of external stimuli such as bacterial products including LPS, as well as cytokines, most importantly tumor necrosis factor-α (TNFα) and interleukin-β (IL1β). Through the synergistic interaction with other transcription factors, further specificity can be achieved while maintaining enormous potential to coordinately induce a large number of functionally related

genes. NF-κB is composed of homo and heterodimers of the Rel protein family and is sequestered in an inactive form in the cytoplasm by members of the IκB family of inhibitory proteins (Ghosh S., May, M. J., and Kopp. E (1998) *Annu. Rev. Immunol.* **16**, 115-260; Zandi, E., and Karin, M. (1999) *Mol. Cell. Biol.* **19**, 4547-4551; Karin, M. (1999) *J. Biol. Chem.* **274**, 27339-27342). IκBs mask the nuclear localization signal on NF-κB, preventing nuclear translocation and hence DNA binding to the promoter regions of responsive genes. Stimulation of cells with an agonist that activates NF-κB leads to a series of biochemical signals, ultimately resulting in the phosphorylation, ubiquitinylation, and degradation of IκBs, thereby releasing NF-κB for nuclear translocation (Ghosh S., May, M. J., and Kopp. E (1998) *Annu. Rev. Immunol.* **16**, 115-260; Zandi, E., and Karin, M. (1999) *Mol. Cell. Biol.* **19**, 4547-4551; Karin, M. (1999) *J. Biol. Chem.* **274**, 27339-27342). Recently, two IκB kinases (IKK1 or IKKα and IKK2 or IKKβ), which phosphorylate IκBs and thereby initiate their degradation, have been cloned and characterized by a number of laboratories (Ghosh S., May, M. J., and Kopp. E (1998) *Annu. Rev. Immunol.* **16**, 115-260; Zandi, E., and Karin, M. (1999) *Mol. Cell. Biol.* **19**, 4547-4551; Karin, M. (1999) *J. Biol. Chem.* **274**, 27339-27342). The catalytic subunits, IKK1 and IKK2, are similar structurally as well as enzymatically and exist as a heterodimer in a large protein complex referred to as the IKK signalsome (Regnier, C., Song, H., Gao, X., Goeddel, D., Cao, Z. and Rothe, M. (1997) *Cell* **90**, 373-383; DiDonato, J.A., Hayakawa, M., Rothwarf, D.M., Zandi, E. and Karin, M. (1997) *Nature* **388**, 548-554; Mercurio, F., Zhu, H., Murray, B.W., Shevchenko, A., Bennett, B.L., Li, J.W., Young, D.B., Barbosa, M., Mann, M., Manning, A. and Roa, A. (1997) *Science* **278**, 860-866; Zandi, E. Rothwarf, D.M., Delhase, M., Hayadawa, M and Karin, M. (1997) *Cell* **91**, 243-252; Woronicz, J.D., Gao, X., Cao, Z., Rothe, M. And Goeddel, D.V. (1997) *Science* **278**, 866-869). A third protein, NEMO (IKKγ, IKKAP1), is a regulatory adapter protein necessary for IKK activation and kinase activity (Yamaoka, S., Courtois, G., Bessia, C., Whiteside, S. T., Weil, R., Agou, F., Kirk, H. E., Kay, R. J., and Ireal, A. (1998) *Cell* **93**, 1231-1240; Rothwarf, D. M., Zandi, E., Natoli, G., Karin, M. (1998) *Nature* **395**, 297; Mercurio, F., Murray, B. W.,

Shevchenko, A., Bennet, B. L., Young, D. B., Li, J. W., Pascual, G., Motiwala, A., Zhu, H., Mann, M and Manning, A. M. (1999) *Mol. Cell. Biol.* **2**, 1526-1538). IKK1 and IKK2 are co-expressed in most human adult tissues as well as in different developmental stages of mouse embryos (Regnier, C., Song, H., Gao, X., Goeddel, D., Cao, Z. and Rothe, M. (1997) *Cell* **90**, 373-383; DiDonato, J.A., Hayakawa, M., Rothwarf, D.M., Zandi, E. and Karin, M. (1997) *Nature* **388**, 548-554; Mercurio, F., Zhu, H., Murray, B.W., Shevchenko, A., Bennett, B.L., Li, J.W., Young, D.B., Barbosa, M., Mann, M., Manning, A. and Roa, A. (1997) *Science* **278**, 860-866; Zandi, E. Rothwarf, D.M., Delhase, M., Hayadawa, M and Karin, M. (1997) *Cell* **91**, 243-252; Woronicz, J.D., Gao, X., Cao, Z., Rothe, M. and Goeddel, D.V. (1997) *Science* **278**, 866-869; Hu, M. C. T., and Wang, Y. (1998) *Gene* **222**, 31-40). This kinase complex appears to represent a critical, common denominator in the activation of NF-κB in a number of signal transduction pathways stimulated by a variety of agonists including cytokines, such as TNFα and IL1β, microbial products such as LPS and viral proteins such as TAX, as well as phorbol esters, oxidizing agents and serine/tyrosine phosphatases (Ghosh S., May, M. J., and Kopp. E (1998) *Annu. Rev. Immunol.* **16**, 115-260; Zandi, E., and Karin, M. (1999) *Mol. Cell. Biol.* **19**, 4547-4551; Karin, M. (1999) *J. Biol. Chem.* **274**, 27339-27342).

[004] IKK1 (also termed IKKα, Regnier, C., Song, H., Gao, X., Goeddel, D., Cao, Z. and Rothe, M. (1997) *Cell* **90**, 373-383; DiDonato, J.A., Hayakawa, M., Rothwarf, D.M., Zandi, E. and Karin, M. (1997) *Nature* **388**, 548-554; Mercurio, F., Zhu, H., Murray, B.W., Shevchenko, A., Bennett, B.L., Li, J.W., Young, D.B., Barbosa, M., Mann, M., Manning, A. And Roa, A. (1997) *Science* **278**, 860-866) was cloned simultaneously by standard biochemical purification of the IκB kinase activity from TNFα stimulated HeLa S3 cells and by its interaction with the MAP3K, NF-κB inducing kinase (NIK), in a yeast two-hybrid screen. IKK1 was identified as the previously cloned serine-threonine kinase, CHUK (Connelly, M. and Marcu, K. (1995) *Cell. Mol. Biol. Res.* **41**, 537-549). IKK1 (also termed IKKα) is an 85 kDa, 745 amino acid protein that contains an N-terminal serine/threonine kinase catalytic domain, a leucine

zipper-like amphipathic helix, and a C-terminal helix-loop-helix domain. IKK2 (also termed IKKβ) was also cloned by standard biochemical purification, copurifying with IKK1 from TNFα stimulated HeLa S3 cells as well as by being identified in the public database from an EST clone with sequence homology to IKK1 (Mercurio, F., Zhu, H., Murray, B.W., Shevchenko, A., Bennett, B.L., Li, J.W., Young, D.B., Barbosa, M., Mann, M., Manning, A. and Roa, A. (1997) *Science* **278**, 860-866; Zandi, E. Rothwarf, D.M., Delhase, M., Hayadawa, M and Karin, M. (1997) *Cell* **91**, 243-252; Woronicz, J.D., Gao, X., Cao, Z., Rothe, M. And Goeddel, D.V. (1997) *Science* **278**, 866-869). IKK2 is an 87 kDa, 756 amino acid protein with the same over all topology as IKK1 except for the addition of an 11 amino acid extension at the C-terminus. IKK1 and IKK2 are 52% identical overall with 65% identity in the kinase domain and 44% identity in the protein interaction domains in the C-terminus. Data obtained using transient mammalian expression analysis, by *in vitro* translation experiments and by coexpression in a baculoviral system reveals that IKK1 and IKK2 associate preferentially as a heterodimer through their leucine zipper motifs. Although homodimers have also been described in these systems, the heterodimer is thought to be the physiologic form of the kinase in mammalian cells (Zandi, E. Rothwarf, D.M., Delhase, M., Hayadawa, M and Karin, M. (1997) *Cell* **91**, 243-252; Li, J., Peet, G.W., Pullen, S.S., Schembri-King, J., Warren, T.C., Marcu, K.B., Kehry, M.R., Barton, R. and Jakes, S. (1998) *J. Biol. Chem.* **273**, 30736-30741). Finally, NEMO (also termed IKKγ) contains three α-helical regions including a leucine zipper, interacts preferentially with IKK2 and is required for activation of the heterodimeric kinase complex perhaps by bringing other proteins into the signalsome complex (Yamaoka, S., Courtois, G., Bessia, C., Whiteside, S. T., Weil, R., Agou, F., Kirk, H. E., Kay, R. J., and Ireal, A. (1998) *Cell* **93**, 1231-1240; Rothwarf, D. M., Zandi, E., Natoli, G., Karin, M. (1998) *Nature* **395**, 297; Mercurio, F., Murray, B. W., Shevchenko, A., Bennet, B. L., Young, D. B., Li, J. W., Pascual, G., Motiwala, A., Zhu, H., Mann, M and Manning, A. M. (1999) *Mol. Cell. Biol.* **2**, 1526-1538).

[005] The kinase activities of IKK1 and IKK2 are regulated by

phosphorylation and require an intact leucine zipper (LZ) for dimerization as well as an intact helix-loop-helix (HLH) domain, which can exert a positive regulatory effect on kinase activity even when it is expressed in trans with the remainder of the IKK protein (Regnier, C., Song, H., Gao, X., Goeddel, D., Cao, Z. and Rothe, M. (1997) *Cell* **90**, 373-383; DiDonato, J.A., Hayakawa, M., Rothwarf, D.M., Zandi, E. and Karin, M. (1997) *Nature* **388**, 548-554; Mercurio,F., Zhu, H., Murray, B.W., Shevchenko, A., Bennett, B.L., Li, J.W., Young, D.B., Barbosa, M., Mann, M., Manning, A. and Roa, A. (1997) *Science* **278**, 860-866; Zandi, E. Rothwarf, D.M., Delhase, M., Hayadawa, M and Karin, M. (1997) *Cell* **91**, 243-252; Woronicz, J.D., Gao, X., Cao, Z., Rothe, M. and Goeddel, D.V. (1997) *Science* **278**, 866-869; Dehase, M., Hayakawa, M., Chen, Y., and Karin, M. (1999) *Science* **284**, 309-313). Both IKK subunits contain a canonical MAPKK activation loop motif near the N- terminus which is the target for phosphorylation and activation of kinase activity by MAP3Ks such as NIK and MEKK1, although the physiologic regulation by these two upstream kinases awaits further characterization (Zandi, E., and Karin, M. (1999) *Mol. Cell. Biol.* **19**, 4547-4551; Karin, M. (1999) *J. Biol. Chem.* **274**, 27339-27342; Karin, M., and Delhase, M. (1998) *Proc. Natl. Acad. Sci.* USA **95**, 9067-9069). Finally, phosphorylation of serines in the C-terminus of IKK2 results in a decrease in IKK activity and it is postulated to be responsible for the transient kinase activity seen after stimulation of cells with an agonist (Dehase, M., Hayakawa, M., Chen, Y., and Karin, M. (1999) *Science* **284**, 309-313).

[006] IKK2 demonstrates a more potent kinase activity compared to IKK1 using IκBα or IκBβ as a substrate (Mercurio, F., Zhu, H., Murray, B.W., Shevchenko, A., Bennett, B.L., Li, J.W., Young, D.B., Barbosa, M., Mann, M., Manning, A. and Roa, A. (1997) *Science* **278**, 860-866; Zandi, E. Rothwarf, D.M., Delhase, M., Hayadawa, M and Karin, M. (1997) *Cell* **91**, 243-252; Woronicz, J.D., Gao, X., Cao, Z., Rothe, M. and Goeddel, D.V. (1997) *Science* **278**, 866-869; Dehase, M., Hayakawa, M., Chen, Y., and Karin, M. (1999) *Science* **284**, 309-313). Mutations of the phospho-acceptor serine residues within the MAPKK activation loop alters IKK2 kinase activity; the serine to

alanine substitutions result in decreased kinase activity whereas the serine to glutamic acid substitutions result in a constitutively active kinase. Similar alanine mutations in IKK1 do not result in a decreased stimulation of total IKK activity in response to TNFα or IL1β (Dehase, M., Hayakawa, M., Chen, Y., and Karin, M. (1999) *Science* **284**, 309-313). IKK2 being the dominant kinase activity within the IKK complex is further supported by the analysis of fibroblasts from mice deficient in IKK1 or IKK2. Fibroblasts lacking IKK1 retain full IKK activity in response to cytokines and could activate NF-κB. In contrast, fibroblasts lacking IKK2 do not exhibit IKK activity when stimulated with cytokines nor do they activate NF-κB. Furthermore, the phenotypes of each IKK knock out is unique with IKK1 deficiency resulting in skin and skeletal defects and IKK2 knock out being embryonic lethal due to hepatocyte apoptosis (Li, Q., Antwerp, D. V., Mercurio, F., Lee, K., and Verma, I. M. (1999) *Science* **284**, 321-325; Takeda, K., Tekeuchi, O., Tsujimura, T., Itami, S., Adachi, O., Kawai, T., Sanjo, H., Yoshikawa, K., Terada, N, and Akira, S. (1999) *Science* **284**, 313-316; Hu, Y., Baud, V., Delhase, M., Zhang, P., Deerinck, T., Ellisman, M., Johnson, R., and Karin, M. (1999) *Science* **284**, 315-320; Li, Q., Lu, Q., Hwang, J. Y., Buscher, D., Lee, K., Izpisua-Belmonte, J. C., and Verma, I. M. (1999) *Gene and Development* **13**, 1322-1328; Tanaka, M., Fuentes, M. E., Yamaguchi, K., Durnin, M. H., Dalrymple, S. A., Hardy, K. L., and Goeddel, D. V. (1999) *Immunity* **10**, 421-429).

[007] It is well-known that NF-KB plays a key role in the regulated expression of a large number of pro-inflammatory mediators including cytokines such as IL-6 and IL-8, cell adhesion molecules, such as ICAM and VCAM, and inducible nitric oxide synthase (iNOS). Such mediators are known to play a role in the recruitment of leukocytes at sites of inflammation and in the case of iNOS, may lead to organ destruction in some inflammatory and autoimmune diseases. The importance of

[008] NF-κB in inflammatory disorders is further strengthened by studies of airway inflammation including asthma in which NF-κB has been shown to be

activated. This activation may underlie the increased cytokine production and leukocyte infiltration characteristic of these disorders. In addition, inhaled steroids are known to reduce airway hyper responsiveness and suppress the inflammatory response in asthmatic airways. In light of the recent findings with regard to glucocorticoid inhibition of NF-κB, one may speculate that these effects are mediated through an inhibition of NF-κB. Further evidence for a role of NF-κB in inflammatory disorders comes from studies of rheumatoid synovium. Although NF-κB is normally present as an inactive cytoplasmic complex, recent immunohistochemical studies have indicated that NF-κB is present in the nuclei, and hence active, in the cells comprising rheumatoid synovium. Furthermore, NF-κB has been shown to be activated in human synovial cells in response to stimulation with TNF-α. Such a distribution may be the underlying mechanism for the increased cytokine and eicosanoid production characteristic of this tissue. See Roshak, A. K., et al., J. Biol. Chem., 271, 31496-31501 (1996).

[009] The NF-κB/Rel and IκB proteins are also likely to play a key role in neoplastic transformation. Family members are associated with cell transformation in vitro and in vivo because of overexpression, gene amplification, gene rearrangements, or translocations (Gilmore TD, *Trends Genet* 7:318-322, 1991; Gillmore TD, *Oncogene* 18:6925-6937, 1999; Rayet B. et al., *Oncogene* 18: 6938-6947, 1991). In addition, rearrangement and/or amplification of the genes encoding these proteins are seen in 20-25% of certain human lymphoid tumors. In addition, a role for NF-κB in the regulation of apoptosis, cell cycle progression, invasion, and metastasis has been reported (Bours V. et al., *Biochemical Pharmacology* 60:1085-1090, 2000) strengthening the role of this transcription factor in the control of cell proliferation. The inhibition of NF-κB has been shown to potentiate TNF- and cancer therapy through increased apoptosis (Wang C-Y et al., *Science* 274:784-787, 1996; Wang C-Y et al., *Nat Med* 5:412-417, 1999). It has also been shown that human T-cell leukemia virus type 1 (HTLV1) infected cells (the etiological agent of an aggressive malignancy of activated $CD4^+$ T lymphocytes), IKKα and IKKβ are

expressed constitutively, which normally function in a transient manner (Chu Z-L et al., *J of Biological Chemistry* 273:15891-15894, 1998). The HTLV1 transforming and transactivating protein (Tax) has been shown to bind MEKK1 and increases the activity of IKKβ to enhance phosphorylation of serine residues in IκBα that lead to its degradation.

[0010] WO 98/02430 and EP 853 083 disclose various 4-pyridyl derivatives, and EP 908 456 discloses various 3-pyrazolyl derivatives.

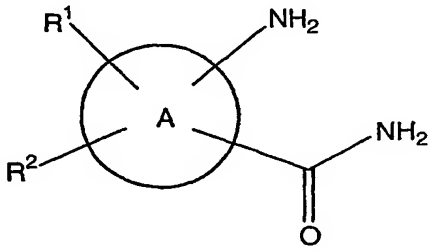
[0011] DE 19725450 discloses various 3-pyridinyl and 5-pyrimidyl derivatives.

[0012] WO 99/46244, WO 9854166, and EP 202 538 disclose a series of substituted thienyl compounds said to possess biological activity.

[0013] WO 01/58890 discloses a series of heteroaromatic carboxamide derivatives, which allegedly are inhibitors of IKK-2.

DETAILED DESCRIPTION OF THE INVENTION

[0014] A class of compounds, which are useful in treating cancer, inflammation, and inflammation related disorders, is defined by Formula I:



wherein

A is a 5-membered heteroaromatic ring containing one or two heteroatoms independently selected from oxygen, nitrogen, or sulfur;

R^1 is selected from the group consisting of: hydrogen, halogen, cyano, nitro, $-N(R^3)_2$, $-CON(R^3)_2$, $-COOR^3$, $-NR^3COR^3$, $S(O)_mR^3$, $-SO_2N(R^3)_2$, $-NR^3SO_2R^3$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, substituted or unsubstituted aryl, and a substituted or unsubstituted 5- to 7-membered heteroaromatic ring containing one to three heteroatoms independently selected from oxygen, nitrogen, or sulfur, wherein said substituent(s) are independently selected from the group consisting of: halogen, cyano, nitro, $-N(R^4)_2$, $-CON(R^4)_2$, $-COOR^4$, $-NR^4COR^4$, $S(O)_mR^4$, $-SO_2N(R^4)_2$, $-NR^4SO_2R^4$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, aminoalkyl, and aryl;

R^2 is selected from the group consisting of: substituted or unsubstituted aryl, and a 5- to 7-membered substituted or unsubstituted heteroaromatic ring containing one to three heteroatoms independently selected from oxygen, nitrogen, or sulfur, wherein said substituent(s) are independently selected from the group consisting of: halogen, cyano, nitro, $-N(R^4)_2$, $-CON(R^4)_2$, $-COOR^4$, $-NR^4COR^4$, $S(O)_mR^4$, $-SO_2N(R^4)_2$, $-NR^4SO_2R^4$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, aminoalkyl, and aryl;

R^1 and R^2 can optionally be taken together form a 5 or 6 membered saturated or unsaturated ring optionally substituted with one or more substituent selected from the group consisting of: halogen, cyano, nitro, $-N(R^3)_2$, $-CON(R^3)_2$, $-COOR^3$, $-NR^3COR^3$, $S(O)_mR^3$, $-SO_2N(R^3)_2$, $-NR^3SO_2R^3$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, substituted or unsubstituted aryl, and a substituted or unsubstituted 5- to 7-membered heteroaromatic ring containing one to three heteroatoms independently selected from oxygen, nitrogen, or

sulfur, wherein said substituent(s) are independently selected from the group consisting of: halogen, cyano, nitro, $-N(R^4)_2$, $-CON(R^4)_2$, $-COOR^4$, $-NR^4COR^4$, $S(O)_mR^4$, $-SO_2N(R^4)_2$, $-NR^4SO_2R^4$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, aminoalkyl, and aryl;

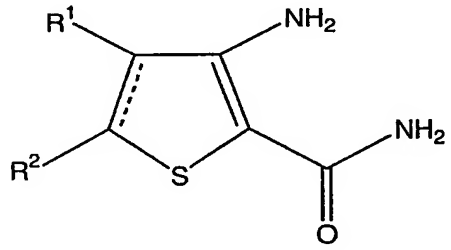
$\mathbf{R^3}$ is selected from the group consisting of: hydrogen or alkyl;

$\mathbf{R^4}$ is selected from the group consisting of: hydrogen or alkyl;

m is an integer 0, 1, or 2; and

isomers, tautomers, carriers, prodrugs, pharmaceutically acceptable salts thereof.

[0015] Another class of compounds is defined by formula II



wherein

$\mathbf{R^1}$ is selected from the group consisting of: hydrogen, halogen, cyano, nitro, $-N(R^3)_2$, $-CON(R^3)_2$, $-COOR^3$, $-NR^3COR^3$, $S(O)_mR^3$, $-SO_2N(R^3)_2$, $-NR^3SO_2R^3$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, substituted or unsubstituted aryl, and a substituted or unsubstituted 5- to 7-membered heteroaromatic ring containing one to three heteroatoms independently selected from oxygen, nitrogen, or

sulfur, wherein said substituent(s) are independently selected from the group consisting of: halogen, cyano, nitro, $-N(R^4)_2$, $-CON(R^4)_2$, $-COOR^4$, $-NR^4COR^4$, $S(O)_mR^4$, $-SO_2N(R^4)_2$, $-NR^4SO_2R^4$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, aminoalkyl, and aryl;

R^2 is selected from the group consisting of: substituted or unsubstituted aryl, and a 5- to 7-membered substituted or unsubstituted heteroaromatic ring containing one to three heteroatoms independently selected from oxygen, nitrogen, or sulfur, wherein said substituent(s) are independently selected from the group consisting of: halogen, cyano, nitro, $-N(R^4)_2$, $-CON(R^4)_2$, $-COOR^4$, $-NR^4COR^4$, $S(O)_mR^4$, $-SO_2N(R^4)_2$, $-NR^4SO_2R^4$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, aminoalkyl, and aryl;

R^1 and R^2 can optionally be taken together form a 5 or 6 membered saturated or unsaturated ring optionally substituted with one or more substituent selected from the group consisting of: halogen, cyano, nitro, $-N(R^3)_2$, $-CON(R^3)_2$, $-COOR^3$, $-NR^3COR^3$, $S(O)_mR^3$, $-SO_2N(R^3)_2$, $-NR^3SO_2R^3$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, substituted or unsubstituted aryl, and a substituted or unsubstituted 5- to 7-membered heteroaromatic ring containing one to three heteroatoms independently selected from oxygen, nitrogen, or sulfur, wherein said substituent(s) are independently selected from the group consisting of: halogen, cyano, nitro, $-N(R^4)_2$, $-CON(R^4)_2$, $-COOR^4$, $-NR^4COR^4$, $S(O)_mR^4$, $-SO_2N(R^4)_2$, $-NR^4SO_2R^4$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, aminoalkyl, and aryl;

R^3 is selected from the group consisting of: hydrogen or alkyl;

R^4 is selected from the group consisting of: hydrogen or alkyl;

m is an integer 0, 1, or 2; and

isomers, tautomers, carriers, prodrugs, pharmaceutically acceptable salts thereof.

Definitions

[0016] The present invention includes the use of all hydrates, solvates, complexes and prodrugs of the compounds of this invention. Prodrugs are any covalently bonded compounds, which release the active parent drug according to Formula I in vivo. If a chiral center or another form of an isomeric center is present in a compound of the present invention all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be covered herein. Compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

[0017] The meaning of any substituent at any one occurrence in Formula I or any sub-formula thereof is independent of its meaning, or any other substituents meaning, at any other occurrence, unless specified otherwise.

[0018] The term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "alkylsulfonyl"; it embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to

about five carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, hexyl, octyl and the, like. The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH_2-) radical. The term "halo" means halogens such as fluorine, chlorine, and bromine or iodine atoms. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl, and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have a bromo, chloro, or a fluoro atom within the radical. Dihalo radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals. The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxylradicals. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro, or bromo, to provide "haloalkoxy" or "haloalkoxyalkyl" radicals. Examples of "alkoxy" radicals include methoxy, butoxy, and trifluoromethoxy. The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two, or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronapthyl, indane, and biphenyl. The term "heterocyclic" embraces saturated, partially saturated, and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclic radicals include pyrrolidyl and morpholinyl. The term "heteroaryl" embraces

unsaturated heterocyclic radicals. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals include thienyl, pyrrolyl, furyl, pyridyl, pyrimidyl, pyrazinyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, and tetrazolyl. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. The term "heterocyclic alkyl" embraces alkyl attached to the heterocyclic. The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals –SO_2–. "Alkylsulfonyl", embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. The term "arylsulfonyl" embraces sulfonyl radicals substituted with an aryl radical. The terms "sulfamyl" or "sulfonamidyl", whether alone or used with terms such as "N-alkylsulfamyl", "N-arylsulfamyl", "N,N-dialkylsulfamyl" and "N-alkyl-N-arylsulfamyl", denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide (–SO_2–NH_2). The terms "N-alkylsulfamyl" and "N,N-dialkylsulfamyl" denote sulfamyl radicals substituted, respectively, with one alkyl radical, a cycloalkyl ring, or two alkyl radicals. The terms "N-arylsulfamyl" and "N-alkyl-N-arylsulfamyl" denote sulfamyl radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical. The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes –CO_2H. The term "carboxyalkyl" embraces radicals having a carboxyradical as defined above, attached to an alkyl radical. The term "carbonyl", whether used alone or with other terms, such as "alkylcarbonyl", denotes –(C=O)–. The term "alkylcarbonyl" embraces radicals having a carbonyl radical substituted with an alkyl radical. An example of an "alkylcarbonyl" radical is CH_3–(C=O)–. The term "alkylcarbonylalkyl" denotes an alkyl radical substituted with an "alkylcarbonyl" radical. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl (C=O) radical. Examples of such "alkoxycarbonyl" radicals include $(CH_3)_3CO$–C=O)– and –(O=)C–OCH_3. The term "alkoxycarbonylalkyl" embraces radicals having "alkoxycarbonyl", as defined above substituted to an alkyl radical. Examples of such "alkoxycarbonylalkyl" radicals include $(CH_3)_3COC$(=O)

$(CH_2)_2$– and –$(CH_2)_2(O=)COCH_3$. The term "amido" when used by itself or with other terms such as "amidoalkyl", "N-monoalkylamido", "N-monoarylamido", "N,N-dialkylamido", "N-alkyl-N-arylamido", "N-alkyl-N-hydroxyamido" and "N-alkyl-N-hydroxyamidoalkyl", embraces a carbonyl radical substituted with an amino radical. The terms "N-alkylamido" and "N,N-dialkylamido" denote amido groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively. The terms "N-monoarylamido" and "N-alkyl-N-arylamido" denote amido radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical. The term "N-alkyl-N-hydroxyamido" embraces amido radicals substituted with a hydroxyl radical and with an alkyl radical. The term "N-alkyl-N-hydroxyamidoalkyl" embraces alkyl radicals substituted with an N-alkyl-N-hydroxyamido radical. The term "amidoalkyl" embraces alkyl radicals substituted with amido radicals. The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals. The term "alkylaminoalkyl" embraces aminoalkyl radicals having the nitrogen atom substituted with an alkyl radical. The term "amidino" denotes an –C(=NH)–NH_2 radical. The term "cyanoamidino" denotes an –C(=N–CN)–NH_2 radical. The term "heterocycloalkyl" embraces heterocyclic-substituted alkyl radicals such as pyridylmethyl and thienylmethyl. The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenethyl, and diphenethyl. The terms benzyl and phenylmethyl are interchangeable. The term "cycloalkyl" embraces radicals having three to ten carbon atoms, such as cyclopropyl cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. The term "cycloalkenyl" embraces unsaturated radicals having three to ten carbon atoms, such as cylopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, and cycloheptenyl. The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. An example of "alkylthio" is methylthio, (CH_3–S–). The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent –S(=O)– atom. The terms "N-alkylamino" and "N, N-dialkylamino" denote amino groups which have been substituted with one alkyl radical and with two

alkyl radicals, respectively. The term "acyl", whether used alone, or within a term such as "acylamino", denotes a radical provided by the residue after removal of hydroxyl from an organic acid. The term "acylamino" embraces an amino radical substituted with an acyl group. An examples of an "acylamino" radical is acetylamino ($CH_3C(=O)$–NH–).

[0019] Compounds of Formula I and II would be useful for, but not limited to, the treatment of inflammation in a subject, and for treatment of other inflammation-associated disorders, such as, as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, compounds of Formula I and II would be useful to treat arthritis, including but not limited to rheumatoid arthritis, spondylo arthopathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus, and juvenile arthritis. Such compounds of Formula I and II would be useful in the treatment of asthma, bronchitis, menstrual cramps, tendinitis, bursitis, and skin related conditions such as psoriasis, eczema, burns, and dermatitis. Compounds of Formula I and II also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, and ulcerative colitis and for the prevention of colorectal cancer. Compounds of Formula I and II would be useful in treating inflammation in such diseases as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, conjunctivitis, swelling occurring after injury, myocardial ischemia, and the like. The compounds are useful as antiinflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects. The compounds of formula I or II are useful as agents for treating cancer or as an anticancer agents. The compounds of formula I or II may be proapoptotic, antiapoptotic, anticell cycle progressive, antiinvasive, and antimetastatic. More specifically, the compounds of this invention are useful in the treatment of a variety of cancers including, but not limited to: carcinoma such as bladder,

breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma; hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoxanthoma, thyroid follicular cancer and Kaposi's sarcoma. Due to the key role of protein kinases in the regulation of cellular proliferation, these compounds are also useful in the treatment of a variety of cell proliferative disorders such as, for instance, benign prostate hyperplasia, familial adenomatosis, polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis. The compounds of formula I or II may be used as an anitviral agent. The compounds of this invention are useful as inhibitors of protein kinases. The compounds of this invention are useful as inhibitors of IKK1 and/or IKK2, IKKα/IKKβ heterodimer, TBK or IKK*i*. The compounds of the invention may also useful as inhibitors of other protein kinases such as, for instance, protein kinase C in different isoforms, cyclin dependent kinase (cdk), Met, PAK-4, PAK-5, ZC-1, STLK-2, DDR-2, Aurora 1, Aurora 2, Bub-1, PLK, Chk1, Chk2, HER2, raf1, MEK1, MAPK, EGF-R, PDGF-R, FGF-R, IGF-R, VEGF-R, PI3K, weel kinase, Src, Abl, Akt, ILK, MK-2, IKK-2, Cdc7, Nek, and thus be effective in the treatment of diseases associated with other protein kinases. The present invention preferably includes compounds, which selectively inhibit IKK2 over IKK1. Preferably, the compounds have an IKK2 IC50 of less than 1 μM, and have a selectivity ratio of IKK2 inhibition over IKK1 inhibition of at least 50,

and more preferably of at least 100. Even more preferably, the compounds have an IKK1 IC50 of greater than 10 μM, and more preferably of greater than 100 μM. The compounds of formula may also be used to treat angiogenesis associated cardiovascular, ophthalmology and osteoporosis disorders. The compounds of the present invention may also be used for treatment of knee injury such as sport injuries.

[0020] While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The present invention comprises a pharmaceutical composition comprising a therapeutically effective amount of a compound of the present invention in association with at least one pharmaceutically acceptable carrier, adjuvant, or diluent. The present invention also comprises a method of treating inflammation or inflammation associated disorders in a subject, the method comprising administering to the subject having such inflammation or disorders a therapeutically effective amount of a compound of the present invention. Also included in the family of compounds of the present invention are the pharmaceutically acceptable salts thereof. The term "pharmaceutically acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically acceptable. Suitable pharmaceutically acceptable acid addition salts of compounds of the present invention may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric, and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicyclic, salicyclic, phydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, stearic,

cyclohexylaminosulfonic, algenic, β-hydroxybutyric, salicyclic, galactaric and galacturonic acid. Suitable pharmaceutically acceptable base addition salts of compounds of the present invention include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methyl-glucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of the present invention by reacting, for example, the appropriate acid or base with the compound of the present invention.

[0021] Also embraced within this invention are pharmaceutical compositions comprising one or more compounds of the present invention in association with one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants and/or excipient (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. Accordingly, the compounds of the present invention may be used in the manufacture of a medicament. Pharmaceutical compositions of the compounds of the present invention prepared as herein before described may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation may be a buffered, isotonic aqueous solution. The compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and composition may, for example, be administered intravascularly, intraperitoneally, intravenously, subcutaneously, intramuscularly, intramedullary, orally, or topically. For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension, or liquid. The active ingredient may also be administered by injection as a composition wherein, for example, normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution may be used as a suitable carrier. Such formulation is

especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride, or sodium citrate. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The amount of therapeutically active compound that is administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely. The pharmaceutical compositions may contain active ingredient in the range of about 0.1 to 2000 mg, preferably in the range of about 0.5 to 500 mg and most preferably between about 1 and 100 mg. A daily dose of about 0.01 to 100 mg/kg bodyweight, preferably between about 0.1 and about 50 mg/kg body weight and most preferably between about 1 to 20 mg/kg bodyweight, may be appropriate. The daily dose can be administered in one to four doses per day. For therapeutic purposes, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered orally, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled release formulation as may be provided in a dispersion of active compound in a sustained release material such as glyceryl monostearate, glyceryl distearate, hydroxypropylmethyl cellulose alone or with a wax. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one

or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion, or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered orally or filled into a soft gelatin capsule. For rectal administration, the compounds of the present invention may also be combined with excipients such as cocoa butter, glycerin, gelatin, or polyethylene glycols and molded into a suppository. The methods of the present invention include topical administration of the compounds of the present invention. By topical administration is meant non-systemic administration, including the application of a compound of the invention externally to the epidermis, to the buccal cavity and instillation of such a compound into the ear, eye, and nose, wherein the compound does not significantly enter the blood stream. By systemic administration is meant oral, intravenous, intraperitoneal, and intramuscular administration. The amount of a compound of the present invention (hereinafter referred to as the active ingredient) required for therapeutic or prophylactic effect upon topical administration will, of course, vary with the compound chosen, the nature and severity of the condition being treated and the animal undergoing treatment, and is ultimately at the discretion of the physician.

[0022] The topical formulations of the present invention, both for veterinary and for human medical use, comprise an active ingredient together with one or more acceptable carriers therefore, and optionally any other therapeutic ingredients. The carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of where

treatment is required such as: liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.01 to 5.0 wt%. of the formulation.

[0023] Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container, which is then sealed and sterilized by autoclaving, or maintaining at 90-100° C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.00217c), benzalkonium chloride (0.0 1%) and chlorhexidine acetate (0.0 1%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol, and propylene glycol.

[0024] Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil. Creams, ointments, or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin

such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as stearic or oleic acid together with an alcohol such as propylene glycol or macrogols. The formulation may incorporate any suitable surface-active agent such as an anionic, cationic, or non-ionic surface-active agent such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin may also be included. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art. Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

GENERAL SYNTHETIC PROCEDURES

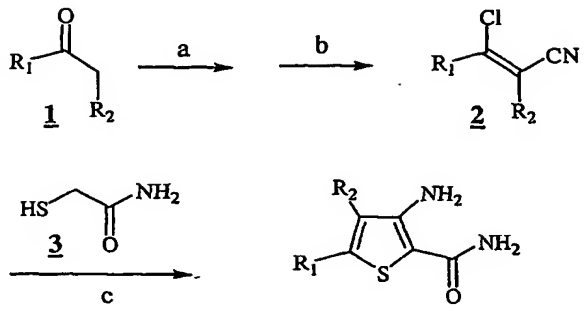
[0025] The starting materials used herein are commercially available or are prepared by routine methods well known to those of ordinary skill in the art and can be found in standard reference books, such as the COMPENDIUM OF ORGANIC SYNTHETIC METHODS, Vol. I-VI (published by Wiley-Interscience).

[0026] The compounds of this invention may be prepared by employing reactions as shown in the schemes below, in addition to other standard manipulations as are known in the literature or exemplified in the experimental procedures. These schemes, therefore, are not limited by the compounds listed or by any particular substituents employed for illustrative purposes.

[0027] Synthetic scheme I shows the preparation of thiophenes from starting material 1. In step 1 of synthetic scheme I, a methyl ketone is treated with phosphorous trichloride in DMF at a reduced temperature followed by hydroxylamine hydrochloride to give a chloroacrylonitrile compound. In step 2 of scheme I, the chloroacrylonitrile is dissolved in a solvent such as an alcohol

and treated with 2-mercaptoacetamide followed by a base such as sodium methoxide.

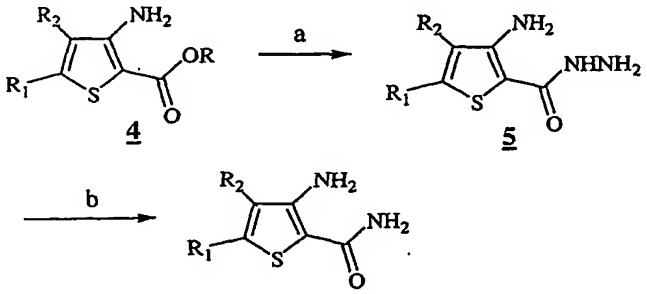
Scheme I



a) PCl_3, DMF; b) $NH_2OH{\cdot}HCl$; c) $NaOCH_3/CH_3OH$

[0028] Synthetic scheme II shows the preparation of amino amide thiophenes from the corresponding ester. In step 1 of synthetic scheme II , an ester is converted to a carbazide with hydrazine. In step 2, the hydrazide is converted to the amide by reducing with Raney nickel.

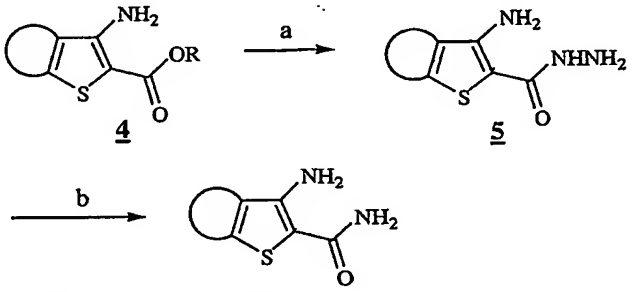
Scheme II



a) N_2H_4; b) raney nickel

[0029] Synthetic scheme III shows the preparation of amino amide thiophenes from the corresponding ester. In step 1 of synthetic scheme III , an ester is converted to a carbazide with hydrazine. In step 2, the hydrazide is converted to the amide by reducing with Raney nickel.

Scheme III



a) N_2H_4; b) raney nickel

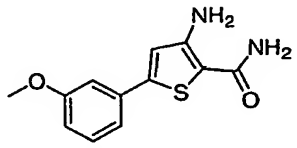
Once the thiophene nucleus has been established, further compounds may be prepared by applying standard techniques for functional group interconversion, well known in the art.

[0030] The complete content of all publications, patents, and patent applications cited in this disclosure are herein incorporated by reference as if each individual publication, patent, or patent application were specifically and individually indicated to incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for the purposes of clarity of understanding, it will be readily apparent to one skilled in the art in light of the teachings of this invention that changes and modifications can be made without departing from the spirit and scope of the present invention. The following examples are provided for exemplification purposes only and are not intended to limit the scope of the invention, which has been described in broad terms above.

Compounds were named using ACD/name software. ACD/name generates IUPAC names rather than CAS names and is not guaranteed to produce the correct IUPAC name in all cases.

EXAMPLES

[0031] Example 1



3-amino-5-(3-methoxyphenyl)thiophene-2-carboxamide

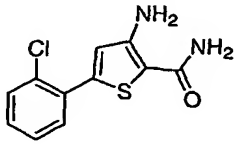
[0032] Step 1: Preparation of 3-chloro-3-(3-methoxyphenyl)prop-2-enenitrile.

A solution of 3'-methoxyacetophenone (10 g, 66.6 mmol) in dimethylformamide (200 ml) under nitrogen was chilled in an ice-water bath. To this solution was added phosphorus trichloride (11.6 mL, 18.3 g, 133 mmol) drop wise. The ice-water bath was removed, and the resulting reaction mixture was stirred under nitrogen for 2 hours. Hydroxylamine hydrochloride (13.9 g, 200 mmol) was added in small portions resulting in an exothermic reaction. The reaction mixture was stirred at room temperature overnight. Saturated aqueous $NaHCO_3$ was added to the reaction mixture, and it was extracted with ethyl acetate 3 X. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrate in vacuo. This material was used without further purification.

[0033] Step 2. Preparation of 3-amino-5-(3-methoxyphenyl)thiophene-2-carboxamide.

2-mercaptoacetamide (18.2 g, 200 mmol) was added to a solution of the material from step 1 in methanol (100 mL) under nitrogen. To this mixture was added a solution of sodium methoxide (7.19 g, 133 mmol) in methanol (200 mL) drop wise. The resulting reaction mixture was stirred at room temperature for 5 hours. Saturated aqueous $NaHCO_3$ was added followed by 1 N HCl until gas evolution was observed. Water was added and the mixture was extracted 3x with ethyl acetate, dried over MgSO4, and filtered. The filtrate was concentrated in vacuo, recrystallized from ethyl acetate/ hexane to yield a white solid (3 g). This material was taken up in methanol and 1 eq. of sodium methoxide in methanol was added. The resulting reaction mixture was stirred at room temperature for 2 hours. The mixture was concentrated. Water and ethyl acetate were added, and the layers were separated. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by chromatography on a silica gel column eluting with 70% ethyl acetate to hexane. The fractions containing the desired product were combined, concentrated, and recrystallized from ethyl acetate/ hexane to afford the title compound as a yellow/orange solid. (1.28 g, 7.7 %): mp 113.8-116.6 °C. ^1H NMR ($CDCl_3$/300 MHz) 7.39-7.30 (m, 3H), 7.15 (d, 1H), 7.10 (t, 1H), 6.95-6.85 (m, 1H), 6.79 (s, 1H), 5.21 (brs, 2H), 3.85 (s, 3H). ES+LRMS *m/z* 249 (M+H). ES+HRMS *m/z* 249.0679 (M+H, $C_{12}H_{12}N_2O_2S$ requires 294.0697). Anal Calcd. for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28. Found: C, 57.85; H, 4.98; N, 11.13.

[0034] Example 2



3-amino-5-(2-chlorophenyl)thiophene-2-carboxamide

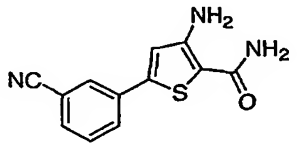
[0035] Step 1. Preparation of 3-chloro-3-(2-chlorophenyl)prop-2-enenitrile.

A solution of 2'-chloroacetophenone (5 g, 32.3 mmol) in DMF (100 mL) under nitrogen was chilled in an ice-water bath. To this cool solution was added drop wise phosphorus trichloride (8.88 g, 64.7 mmol). Upon complete addition of the PCl_3, the ice-water bath was removed, and the resulting reaction mixture was stirred under nitrogen for 2 hours. Then hydroxylamine hydrochloride (6.74 g, 97.0 mmol) was added in small portions resulting in an exothermic reaction. The reaction mixture was stirred at room temperature overnight. Ethyl acetate was added, and the layers were separated. The organic phase was washed 3x with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. This material was used in the next reaction without further purification.

[0036] Step 2. Preparation of 3-amino-5-(2-chlorophenyl)thiophene-2-carboxamide.

2-mercaptoacetamide (8.83 g, 97.0 mmol) was added to a solution of the material from step 1 in methanol (50 mL) under nitrogen. To this mixture was added sodium methoxide in methanol (0.5 M, 388 mL, 194 mmol) drop wise. The reaction mixture was stirred at room temperature for 72 h. The reaction was concentrated in vacuo and water was added. A solid was filtered and washed with water several times to afford the title compound as solid. (2.24 g, 27 %): mp 129.6-129.7 °C. ^{1}H NMR ($CDCl_3$/300 MHz) 7.58-7.45 (m, 2H), 7.38-7.22 (m, 5H), 6.88 (d, 2H). ES+LRMS *m/z* 253 (M+H). ES+HRMS *m/z* 253.0204 (M+H, $C_{11}H_9N_2OSCl$ requires 253.0202). Anal Calcd. for $C_{11}H_9N_2OSCl + H_2O$: C, 48.80; H, 4.10; N, 10.35. Found: C, 48.62; H, 3.85; N, 10.29.

[0037] Example 3



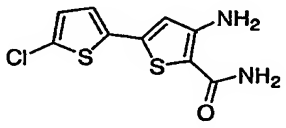
3-amino-5-(3-cyanophenyl)thiophene-2-carboxamide

[0038] Step 1. Prepared by using the procedures found in example 2, step1.

[0039] Step 2. Preparation of 3-amino-5-(3-cyanophenyl)thiophene-2-carboxamide.

2-mercaptoacetamide (5.65 g, 62.1 mmol) was added to a solution of the material from step 1 (20.7 mmol) in methanol (100 mL) under nitrogen. To this mixture was added a solution of sodium methoxide in methanol (0.5M, 166 mL, 82.8 mmol) drop wise. After stirring at room temperature overnight, the reaction mixture was concentrated in vacuo to half its volume, and water was added. A solid was filtered, washed with water several times, and recrystallized from ethyl acetate/hexane to afford the title compound as a solid. (2.61 g, 52 %): mp 193.2-193.5 °C. ^{1}H NMR ($CDCl_3$/300 MHz) 7.78-7.66 (m, 2H), 7.55-7.46 (m, 1H), 7.46-7.36 (m, 1H), 6.78 (m, 1H), 3.84 (brs, 4H). ES+LRMS *m/z* 244 (M+H). ES+HRMS *m/z* 244.0538 (M+H, $C_{12}H_9N_3OS$ requires 244.0545). Anal. Calcd. for $C_{12}H_9N_3OS$: C, 59.24; H, 3.73; N, 17.27. Found: C, 58.27; H, 3.92; N, 17.10.

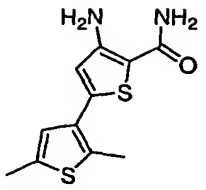
[0040] Example 4



4-amino-5'-chloro-2,2'-bithiophene-5-carboxamide

The title compound was prepared using the procedures found in example 3: mp 185.6-188.3 °C. ^{1}H NMR ($CDCl_3$/300 MHz) 7.25 (s, 1H), 6.96 (d, 1H), 6.80 (d, 1H), 6.59 (s, 1H), 3.40 (brs, 3H). ES+LRMS *m/z* 259 (M+H). ES+HRMS *m/z* 258.9761 (M+H, $C_9H_7N_2OS_2Cl$ requires 258.9767). Anal. Calcd. for $C_9H_7N_2OS_2Cl$: C, 41.78; H, 2.73; N,10.83. Found: C, 41.13; H, 2.87; N, 10.68.

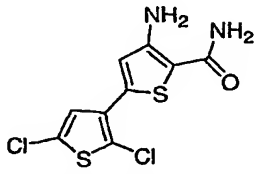
[0041] Example 5



4-amino-2',5'-dimethyl-2,3'-bithiophene-5-carboxamide

The title compound was prepared using the procedures found in example 3: mp 151.4-152.3 °C. ^{1}H NMR ($CDCl_3$/300 MHz) 7.26 (s, 2H), 6.76 (s, 1H), 6.54 (s, 1H), 5.19 (brs, 2H), 2.52 (s, 3H), 2.42 (s, 3H). FAB+LRSM *m/z* 253 (M+H). ES+HRMS *m/z* 253.0462 (M+H, $C_{11}H_{12}N_2OS_2$ requires 253.0469). Anal. Calcd. for $C_{11}H_{12}N_2OS_2$: C, 52.36; H, 4.79; N, 11.10. Found: C, 52.12; H, 4.97; N, 11.01.

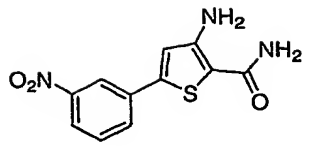
[0042] Example 6



4-amino-2',5'-dichloro-2,3'-bithiophene-5-carboxamide

The title compound was prepared using the procedures found in example 3: mp 175.2-176.4 °C. ^{1}H NMR (CD_3OD/300 MHz) 7.21 (s, 1H), 7.05 (s, 1H), 4.90 (brs, 4H). FAB+LRMS *m/z* 293 (M+H). ES+HRMS *m/z* 292.9392 (M+H, $C_9H_6N_2OS_2Cl_2$ requires 292.9397. Anal Calcd. for $C_9H_6N_2OS_2Cl_2$: C, 36.87; H, 2.06; N, 9.55. Found: C, 36.53; H, 2.15; N, 9.36.

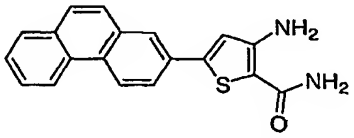
[0043] Example 7



3-amino-5-(3-nitrophenyl)thiophene-2-carboxamide

The title compound was prepared using the procedures found in example 3: mp 210.5-210.9 °C. ^{1}H NMR (DMSO-d_6/300 MHz) 8.31 (t, 1H), 8.23-8.14 (m, 1H), 8.08-7.98 (m, 1H), 7.79-7.68 (m, 1H), 7.15 (s, 1H), 7.02 (brs, 2H), 6.53 (brs, 2H). FAB+LRSM *m/z* 264 (M+H). ES+HRMS *m/z* 264.0456 (M+H, $C_{11}H_9N_3O_3S$ requires 264.0443).

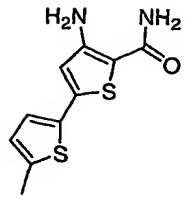
[0044] Example 8



3-amino-5-(2-phenanthryl)thiophene-2-carboxamide

The title compound was prepared using the procedures found in example 3: mp >300 °C. ^{1}H NMR (DMSO-d_6/300 MHz) 8.96-8.77 (m, 2H), 8.21 (s, 1H), 8.06-7.83 (m, 4H), 7.76-7.60 (m, 2H), 7.14 (s, 1H), 6.97 (brs, 2H), 6.53 (brs, 2H). ES+LRMS *m/z* 319 (M+H). ES+HRMS *m/z* 319.0909 (M+H, $C_{19}H_{14}N_2OS$ requires 319.0905).

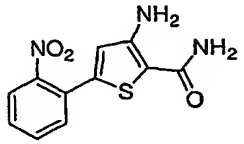
[0045] Example 9



4-amino-5'-methyl-2,2'-bithiophene-5-carboxamide

The title compound was prepared using the procedures found in example 3: mp 205.6-206.4 °C. ^{1}H NMR (CD_3CN/300 MHz) 7.10 (d, 1H), 6.76 (d, 1H), 6.68 (s, 1H), 5.91 (brs, 1H), 5.64 (brs, 2H), 2.49 (s, 3H), 2.20-2.00 (m, 1H). ES+LRMS *m/z* 239 (M+H). ES+HRMS *m/z* 239.0329 (M+H, $C_{10}H_{10}N_2OS_2$ requires 239.0313).

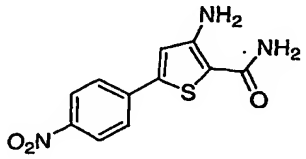
[0046] Example10



3-amino-5-(2-nitrophenyl)thiophene-2-carboxamide

The title compound was prepared using the procedures found in example 3: ^{1}H NMR (DMSO-d_6/300 MHz) 7.98-7.88 (m, 1H), 7.77-7.57 (m, 3H), 6.96 (s, 2H), 6.59 (brs, 1H), 6.50 (brs, 2H). ES+LRMS *m/z* 264 (M+H). ES+HRMS *m/z* 264.0435 (M+H, $C_{11}H_9N_3O_3S$ requires 264.0443). Anal Calcd. for $C_{11}H_9N_3O_3S$: C, 50.18; H, 3.45; N, 15.96. Found: C, 50.15; H 3.38; N, 15.99.

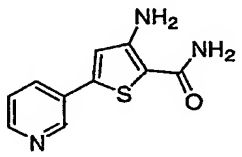
[0047] Example 11



3-amino-5-(4-nitrophenyl)thiophene-2-carboxamide

The title compound was prepared using the procedures found in example 3: ^{1}H NMR (DMSO-d_6/300 MHz) 8.28 (d, 2H), 7.84 (d, 2H), 7.15 (s, 1H), 7.05 (brs, 2H), 6.54 (brs, 2H). ES+LRMS *m/z* 264 (M+H). ES+HRMS *m/z* 264.0434 (M+H, $C_{11}H_9N_3O_3S$ requires 264.0443).

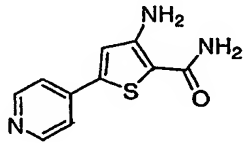
[0048] Example 12



3-amino-5-pyridin-3-ylthiophene-2-carboxamide

The title compound was prepared using the procedures found in example 3: mp 207.3-207.5 °C. ^{1}H NMR (DMSO-d_6/300 MHz) 8.80 (d, 1H), 8.53 (m, 1H), 8.03-7.88 (m, 1H), 7.55-7.37 (m, 1H), 7.13-6.84 (m, 3H), 6.51 (brs, 2H). ES+LRMS *m/z* 220 (M+H). ES+HRMS *m/z* 220.0527 (M+H, $C_{10}H_9N_3OS$ requires 220.0545).

[0049] Example 13

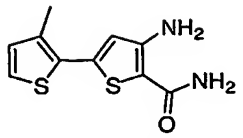


3-amino-5-pyridin-4-ylthiophene-2-carboxamide

The title compound was prepared using the procedures found in example 3: mp 245.8-246.7 °C. ^{1}H NMR (DMSO-d_6/300 MHz) 8.62 (m, 2H), 7.55 (m, 2H), 7.19 (s, 1H), 7.07 (brs, 2H), 6.55 (brs, 2H). ES+LRMS *m/z* 220 (M+H). ES+HRMS *m/z* 220.0547 (M+H, $C_{10}H_9N_3OS$ requires 220.0545). Anal Calcd.

for $C_{10}H_9N_3OS$: C, 54.78; H, 4.14; N, 19.16. Found: C, 54.26; H, 4.04; N, 19.24.

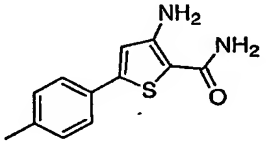
[0050] Example 14



4-amino-3'-methyl-2,2'-bithiophene-5-carboxamide

The title compound was prepared using the procedures found in example 3: mp 161.9-161.9 °C. ^{1}H NMR (DMSO-d_6/300 MHz) 7.47 (d, 1H), 7.09-6.82 (m, 3H), 6.71 (s, 1H), 6.48 (brs, 2H), 2.37 (s, 3H). ES+LRMS *m/z* 239 (M+H). ES+HRMS *m/z* 239.0332 (M+H, $C_{10}H_{10}N_2OS_2$ requires 239.0313).

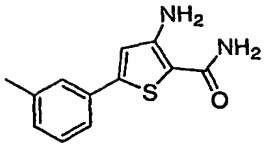
[0051] Example 15



3-amino-5-(4-methylphenyl)thiophene-2-carboxamide

The title compound was prepared using the procedures found in example 3: mp 254.3-254.8 °C. ^{1}H NMR (DMSO-d_6/300 MHz) 7.49 (d, 2H), 7.26 (d, 2H), 6.88 (m, 3H), 6.46 (s, 2H), 2.33 (s, 3H). ES+LRMS *m/z* 233 (M+H). ES+HRMS *m/z* 233.0765 (M+H, $C_{12}H_{12}N_2OS$ requires 233.0749). Anal Calcd. for $C_{12}H_{12}N_2OS$: C, 62.04; H, 5.21; N, 12.06. Found: C, 62.09; H, 5.16; N, 11.98.

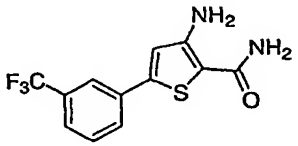
[0052] Example 16



3-amino-5-(3-methylphenyl)thiophene-2-carboxamide

The title compound was prepared using the procedures found in example 3: mp 193.3-194.1 °C. ^{1}H NMR (DMSO-d_6/300 MHz) 7.46-7.27 (m, 3H), 7.19 (d, 1H), 6.99-6.80 (m, 3H), 6.47 (s, 2H), 2.35 (s, 3H). ES+LRMS *m/z* 233 (M+H). ES+HRMS *m/z* 233.0750 (M+H, $C_{12}H_{12}N_2OS$ requires 233.0749). Anal Calcd for $C_{12}H_{12}N_2OS$ + 1/2H_2O: C, 59.73; H, 5.43; N, 11.61. Found: C, 60.35; H, 4.99; N, 11.73.

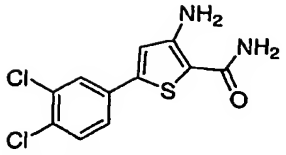
[0053] Example 17



3-amino-5-[3-(trifluoromethyl)phenyl]thiophene-2-carboxamide

The title compound was prepared using the procedures found in example 3: mp 166.6-167.2 °C. ^{1}H NMR (DMSO-d_6/300 MHz) 7.94-7.81 (m, 2H), 7.78-7.63 (m, 2H), 7.11 (s, 1H), 6.97 (s, 2H), 6.50 (s, 2H). ES+LRMS *m/z* 287 (M+H). ES+HRMS *m/z* 287.0468 (M+H, $C_{12}H_9N_2OF_3S$ requires 287.0466). Anal Calcd for $C_{12}H_9N_2OF_3S$: C, 50.35; H, 3.17; N, 9.79. Found: C, 50.48. H, 3.05; N, 9.60.

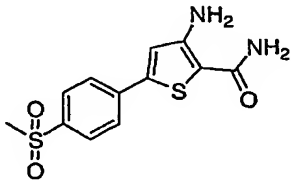
[0054] Example 18



3-amino-5-(3,4-dichlorophenyl)thiophene-2-carboxamide

The title compound was prepared using the procedures found in example 3: mp 217.0-217.1 °C. ^{1}H NMR (DMSO-d_6/300 MHz) 7.83 (s, 1H), 7.70 (d, 1H), 7.63-7.48 (m, 1H), 7.12-6.86 (m, 3H), 6.50 (s, 2H). ES+LRMS *m/z* 287 (M+H). ES+HRMS *m/z* 286.9818 (M+H, $C_{11}H_8N_2OSCl_2$ requires 286.9813). Anal Calcd for $C_{11}H_8N_2OSCl_2$: C, 46.01; H, 2.81; N, 9.76. Found: C, 45.88; H, 2.67; N, 9.74.

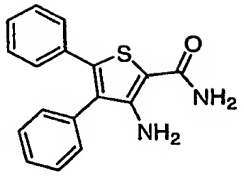
[0055] Example 19



3-amino-5-[4-(methylsulfonyl)phenyl]thiophene-2-carboxamide

The title compound was prepared using the procedures found in example 3: ^{1}H NMR (DMSO-d_6/300 MHz) 7.99 (s, 2H), 7.84 (d, 2H), 7.13 (s, 1H), 7.03 (s, 1H), 6.53 (d, 1H), 3.25 (brs, 2H), 3.20 (s, 3H). ES+LRMS *m/z* 297 (M+H). ES+HRMS *m/z* 297.0377 (M+H, $C_{12}H_{12}N_2O_3S_2$ requires 297.0368). Anal Calcd for $C_{12}H_{12}N_2O_3S_2$: C, 48.63; H, 4.08; N, 9.45. Found: C, 48.17; H, 3.83; N, 9.34.

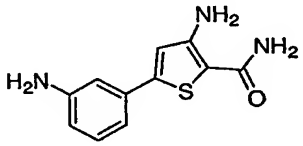
[0056] Example20



3-amino-4,5-diphenylthiophene-2-carboxamide

The title compound was prepared using the procedures found in example 3: mp 208.4-208.9 °C. ^{1}H NMR (DMSO-d_6/300 MHz) 7.49-6.96 (m, 11H), 5.99 (brs, 2H), 3.32 (brs, 1H). ES+LRMS *m/z* 295 (M+H). ES+HRMS *m/z* 295.0913 (M+H, $C_{17}H_{14}N_2OS$ requires 295.0905). Anal Calcd for $C_{17}H_{14}N_2OS$: C, 69.36; H, 4.79; N, 9.52. Found: C, 69.55; H, 4.41; N, 9.39.

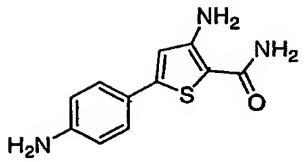
[0057] Example 21



3-amino-5-(3-aminophenyl)thiophene-2-carboxamide

[0058] The product of example 7, 3-amino-5-(3-nitrophenyl)thiophene-2-carboxamide (1 g, 3.80 mmol), triethylamine (20 mL) and 10 % palladium on carbon were heated to boiling followed by the drop wise addition of formic acid (0.75 g, 16.3 mmol). The resulting mixture was heated at reflux 3 hours. The reaction was cooled and filtered through a plug of Celite eluting with methanol. The filtrate was concentrated in vacuo and purified by silica gel chromatography eluting with 5% methanol / dichloromethane. The fractions containing the desired product were concentrated to yield a yellow solid. The solid was washed with methanol to yield a yellow solid. (746 Mg): 225.3-229.4 °C. ^{1}H NMR (DMSO-d_6/300 MHz) 7.05 (t, 1H), 6.92-6.66 (m, 5H), 6.60-6.35 (m, 3H), 5.27 (s, 2H). ES+LRMS *m/z* 234 (M+H). ES+HRMS *m/z* 234.0702 (M+H, $C_{11}H_{11}N_3OS$ requires 234.0701).

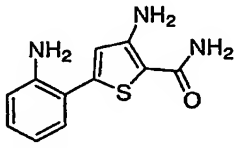
[0059] Example 22



3-amino-5-(4-aminophenyl)thiophene-2-carboxamide

The title compound was prepared using the procedures found in example 21: mp 235.8-241.0 °C. ^{1}H NMR (DMSO-d_6/300 MHz) 7.25 (d, 2H), 6.77-6.51 (m, 5H), 6.40 (brs, 2H), 5.46 (brs, 2H). ES+LRMS *m/z* 234 (M+H). ES+HRMS *m/z* 234.0744 (M+H, $C_{11}H_{11}N_3OS$ requires 234.0701).

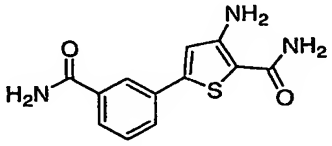
[0060] Example 23



3-amino-5-(2-aminophenyl)thiophene-2-carboxamide

The title compound was prepared using the procedures found in example 21: mp 149.9-150.3 °C. ^{1}H NMR (DMSO-d_6/300 MHz) 7.17-6.97 (m, 2H), 6.89-6.68 (m, 4H), 6.65-6.52 (m, 1H), 6.42 (brs, 2H), 5.12 (brs, 2H). ES+LRMS *m/z* 234 (M+H). ES+HRMS *m/z* 234.0700 (M+H, $C_{11}H_{11}N_3OS$ requires 234.0701).

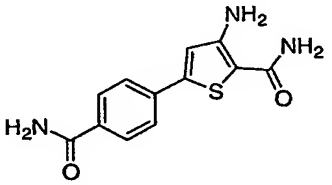
[0061] Example 24



3-amino-5-[3-(aminocarbonyl)phenyl]thiophene-2-carboxamide

[0062] The product of example 3, 3-amino-5-(3-cyanophenyl)thiophene-2-carboxamide (200 mg, 0.82 mmol) and sulfuric acid (3 mL) were heated on a steam bath for 30 minutes. The reaction mixture was poured into ice/water (50 mL) and stirred for 1 hour. After neutralizing with $NaHCO_3$, the mixture was extracted 3x with ethyl acetate. The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The solid material was triturated with ethyl acetate and filtered to afford the desired product (50 mg): mp 242.0-242.3 °C. ^{1}H NMR (DMSO-d_6/300 MHz) 8.18-7.99 (m, 2H), 7.83 (d, 1H), 7.70 (d, 1H), 7.59-7.33 (m, 2H), 7.11-6.80 (m,3H), 6.49 (brs, 2H). FAB+LRMS *m/z* 262 (M+H). ES+HRMS *m/z* 262.0649 (M+H, $C_{12}H_{11}N_3O_2S$ requires 262.0650). Anal Calcd for $C_{12}H_{11}N_3O_2S$: C, 55.16; H, 4.24; N, 16.08. Found: C, 54.59; H, 4.15; N, 15.78.

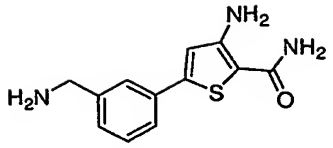
[0063] Example 25



3-amino-5-[4-(aminocarbonyl)phenyl]thiophene-2-carboxamide

The title compound was prepared using the procedures found in example 24. ^{1}H NMR (DMSO-d_6/300 MHz) 8.10-7.82 (m, 3H), 7.66 (d, 2H), 7.41 (brs, 1H), 7.13-6.82 (m, 3H), 6.49 (brs, 2H). ES+LRMS *m/z* 262 (M+H). ES+HRMS *m/z* 262.0669 (M+H, $C_{12}H_{11}N_3O_2S$ requires 262.0650). Anal Calcd for $C_{12}H_{11}N_3O_2S$: C, 55.16; H, 4.24; N, 16.08. Found: C, 54.83; H 4.29; N, 15.63.

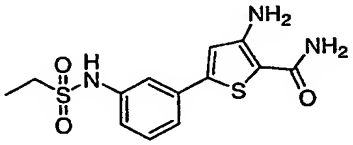
[0064] Example 26



3-amino-5-[3-(aminomethyl)phenyl]thiophene-2-carboxamide

A par reaction bottle was charged with 3-amino-5-(3-cyanophenyl)thiophene-2-carboxamide (1 g, 4.12 mmol), 10 % palladium on carbon, and methanol (40 mL). The par bottle was pressurized to 40 psi and stirred at room temperature for 3 days. The mixture was filtered through a plug of Celite eluting with methanol. The filtrate was concentrated in vacuo and recrystallized with ethyl acetate/ hexane to give the title compound as a yellow solid (168 mg): mp 182.1-185.0 °C. ^{1}H NMR (CD_3OD/300 MHz) 7.63 (s, 1H), 7.58-7.47 (m, 1H), 7.43-7.29 (m, 2H), 6.92 (m, 1H), 4.84 (brs, 6H), 3.80 (s, 2H). ES+LRMS *m/z* 248 (M+H). ES+HRMS *m/z* 248.0856 (M+H, $C_{12}H_{13}N_3OS$ requires 248.0858).

[0065] Example 27

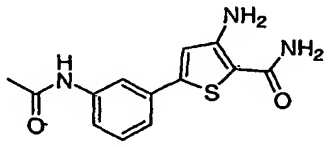


3-amino-5-{3-[(ethylsulfonyl)amino]phenyl}thiophene-2-carboxamide

The product of example 21, 3-amino-5-(3-aminophenyl)thiophene-2-carboxamide, (1.16 g, 4.98 mmol), dichloromethane (20 mL), and pyridine (20 mL) were stirred at room temperature. To this mixture was added ethylsulfonyl chloride (500 µM, 0.67 g, 5.23 mmol) drop wise. After stirring at room temperature for 3 hours, water was added, and the mixture was extracted 3x with ethyl acetate. The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. This material was chromatographed on a silica gel column eluting with ethyl acetate. The fractions containing the desired product were combined and concentrated in vacuo to afford a solid (17.1 mg) :

mp 240.2-240.7 °C. ^{1}H NMR (DMSO-d_6/300 MHz) 9.96 (s, 1H), 7.58-7.11 (m, 4H), 6.91 (d, 3H), 6.50 (s, 2H), 3.13 (q, 2H), 1.20 (q, 3H). ES+LRMS *m/z* 326 (M+H). ES+HRMS *m/z* 326.0626 (M+H, $C_{13}H_{15}N_3O_3S_2$ requires 326.0633).

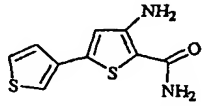
[0066] Example 28



5-[3-(acetylamino)phenyl]-3-aminothiophene-2-carboxamide

The title compound was prepared using the procedures found in Example 27: mp 230.9-233.4 °C. ^{1}H NMR (DMSO-d_6/300 MHz) 10.06 (s, 1H), 7.94 (s, 1H), 7.54-7.17 (m, 3H), 6.87 (d, 3H), 6.47 (s, 2H), 2.05 (s, 3H). ES+LRMS *m/z* 276 (M+H). ES+HRMS *m/z* 276.0776 (M+H, $C_{13}H_{13}N_3O_2S$ requires 276.0807).

[0067] Example 29

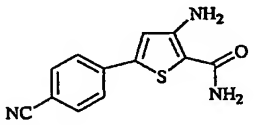


3-amino-5-(3-thienyl)thiophene-2-carboxamide

3-acetylthiophene (100 mmol, 12.62 g) and N, N'-dimethylformamide (200 mL) were stirred at 0° C. Phosphorous trichloride (200 mmol, 27.47 g) was added drop-wise maintaining the temperature below 20° C. After the addition was complete, the mixture was allowed to warm to room temperature and stir for three hours. After re-cooling to 0° C, hydroxylamine hydrochloride (300 mmol, 20.85 g) was added in small portions maintaining the temperature below 20° C. The mixture was allowed to warm to room temperature and stir for one hour. After concentrating to 50 mL, ethyl acetate (200 mL) was added and the mixture washed with brine. Saturated aqueous sodium bicarbonate solution was added

until gas evolution ceased. The layers were separated and the organics were washed with brine two times. After drying over magnesium sulfate, the mixture was concentrated and dissolved in methanol (250 mL). 2-mercaptoacetamide (300 mmol, 27.34 g) was added, followed by sodium methoxide (25 wt%, 200 mmol, 43.22 g) drop-wise. The mixture was allowed to stir until all of the materials dissolved. Saturated aqueous sodium bicarbonate (100 mL) was added followed by hydrochloric acid (1 N) until gas evolution was observed. Water was added to a total volume on 1L and the mixture was allowed to stand 16 h. A light brown solid was collected by filtration. (14.3 g, 64%): mp 208.5-210.9 °C. ^{1}H NMR (DMSO-d_6/300 MHz) 7.7 (m, 1H), 7.61 (m, 1H), 7.3 (m, 1H), 6.8 (bs, 2H), 6.7 (s, 1H), 6.4 (bs, 2H). ESHRMS *m/z* 225.016 (M+H, $C_9H_8N_2OS$ requires 225.016).

[0068] Example 30



3-amino-5-(4-cyanophenyl)thiophene-2-carboxamide

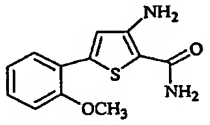
[0069] Step 1: Preparation of 4-[1-chloro-2-cyanoethenyl]benzonitrile.

4-acetylbenzonitrile (10 mmol, 1.45 g) was stirred in N, N'-dimethylformamide (10 mL) at room temperature. Phosphorous trichloride was added drop-wise with a large exotherm. After stirring for one hour, hydroxylamine hydrochloride was added in small portions. After stirring for 16 h, ethyl acetate (100 mL) was added and the mixture washed with brine, saturated aqueous sodium bicarbonate and brine 2 X. After drying over magnesium sulfate and concentrating, a tan solid was obtained by crystallization from ethyl acetate / hexanes. (1.6 g, 85%): mp 157.5-159.0 °C. ^{1}H NMR (DMSO-d_6/300 MHz) 7.97 (m, 4H), 7.67 (dd, 1H), 7.10 (s, 1H).

[0070] Step 2: Preparation of 3-amino-5-(4-cyanophenyl)thiophene-2-carboxamide.

4-[1-chloro-2-cyanoethenyl]benzonitrile (2 mmol, 377 Mg) was stirred at room temperature in methanol (25 mL). Sodium methoxide (25 wt%, 4 mmol, 864 Mg) was added followed immediately by 2-mercaptoacetamide (6 mmol, 547 Mg). After one hour, water (100 mL) was added and a yellow-orange solid was filtered. (230 Mg, 47%): mp 250.4-251.6 °C. ^{1}H NMR (DMSO-d_6/300 MHz) 7.86 (d, J = *8.8* Hz, 2H), 7.73 (d, J = *8.8* Hz, 2H), 7.08 (s, 1H), 7.00 (bs, 2H), 6.48 (bd, 2H). ESHRMS *m/z* 244.057 ($C_{12}H_9N_3OS$ requires 244.054).

[0071] Example 31

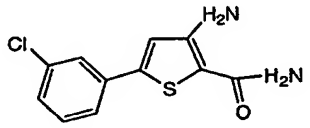


3-amino-5-(2-anisyl)-thiophene-2-carboxamide

2'-methoxyacetophenone (10 mmol, 1.5 g) was stirred in N, N'-dimethylformamide (15 mL) at room temperature. Phosphorous trichloride (20 mmol, 2.75 g) was added drop-wise. After stirring for two hours, hydroxylamine hydrochloride (30 mmol, 2.08 g) was added in small portions. After one hour, the mixture was concentrated and ethyl acetate (100 mL) was added. After washing successively with brine, saturated aqueous sodium bicarbonate, and brine, the mixture was dried over magnesium sulfate and concentrated. Methanol (50 mL) was added followed by 2-mercaptoacetamide (30 mmol, 2.73 g). This mixture was stirred at room temperature when sodium methoxide (25 wt%, 20 mmol, 4.32 g) was added drop-wise. After two hours, saturated aqueous sodium bicarbonate was added followed by 1 N hydrochloric acid until gas evolution was observed. Water was added to a total volume of 500 mL and the mixture was allowed to stand for 16 hours. A yellow solid was filtered and recrystallized from N, N'-dimethylformamide / water. (1.1 g, 44%):

mp 155.2-155.3 °C. ^{1}H NMR (DMSO-d_6/300 MHz) 7.55 (dd, 1H), 7.31 (m, 1H), 7.11 (d, 1H), 7.00 (s, 1H), 6.98 (d, 1H), 6.81 (bs, 2H), 6.33 (bd, 2H), 3.86 (s, 3H). ESHRMS *m/z* 249.070 ($C_{12}H_{12}N_2O_2S$ requires 249.068).

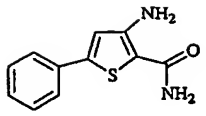
[0072] Example 32



3-amino-5-(3-chlorophenyl)thiophene-2-carboxamide

3'-chloroacetophenone (10 mmol, 1.5 g) was stirred in N, N'-dimethylformamide (15 mL) at 0° C. Phosphorous trichloride (20 mmol, 2.75 g) was added drop-wise. After removing the cooling bath and stirring for two hours, the mixture was again cooled to 0° C and hydroxylamine hydrochloride (30 mmol, 2.08 g) was added in small portions. After stirring for 16 hours at room temperature, the mixture was concentrated and ethyl acetate (150 mL) was added. After washing with brine 3 X, the mixture was dried over magnesium sulfate and concentrated. Methanol (50 mL) was added followed by 2-mercaptoacetamide (30 mmol, 2.73 g). This mixture was stirred at room temperature when sodium methoxide (25 wt%, 20 mmol, 4.32 g) was added drop-wise. When all of the starting materials dissolved, saturated aqueous sodium bicarbonate was added followed by 1 N hydrochloric acid until gas evolution was observed. Water was added to a total volume of 400 mL and the mixture was allowed to stand for 16 hours. A tan solid was filtered. (1.6 g, 63%): mp 168.4-171.3 °C. ^{1}H NMR (DMSO-d_6/300 MHz) 7.58 (m, 1H), 7.50 (m, 1H), 7.41 (m, 2H), 6.98 (s, 1H), 6.81 (bs, 2H), 6.44 (bd, 2H). ESHRMS *m/z* 253.021 ($C_{11}H_9N_2O_2SCl$ requires 253.020).

[0073] Example 33



3-Amino-5-phenyl thiophene-2-carboxamide

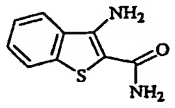
[0074] Step 1: Preparation of 3-amino-5-phenylthiophene-2-carbohydrazide.

Methyl-3-amino-5-phenylthiophene-2-carboxylate (0.250 g, 1.07 mmol) was added to hydrazine monohydrate (5 mL) and heated at 80 °C for three hours. The reaction mixture was cooled to room temperature, and the resulting solid was filtered and washed with water (0.195 g, 78%). ^{1}H nmr (DMSO / 300 MHz) 7.56-7.55 (m, 2H); 7.44-7.31 (m, 3H); 6.92 (s, 1H); 6.44 (s, br, 2H). ESHRMS (*m/z*) 234.0718 (M+H, $C_{11}H_{11}N_3OS$ requires 234.0701).

[0075] Step 2: Preparation of 3-Amino-5-phenyl thiophene-2-carboxamide.

3-amino-5-phenylthiophene-2-carbohydrazide (0.150 g, 0.643 mmol) was dissolved in hot ethanol (10 mL). Raney Nickel (0.5 mL, of a 50/50 wt% slurry in water) was added. After heating at reflux for 16 hours, the mixture was filtered while hot through celite, and rinsed with ethanol and concentrated. (10 mL) 24 mg (17%). ^{1}H nmr (DMSO / 300 MHz) 7.60-7.58 (m, 2H); 7.47-7.34 (m, 3H); 6.94 (s, 1H); 6.91 (s, 2H). ESHRMS (*m/z*) 219.0575 (M+H $C_{11}H_{10}N_2OS$ requires 219.0592).

[0076] Example 34

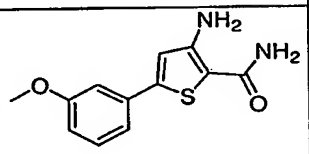
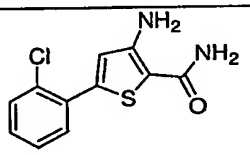
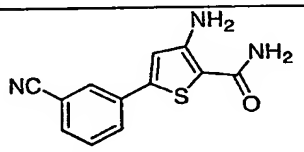
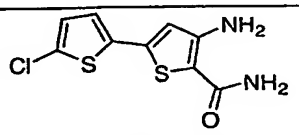
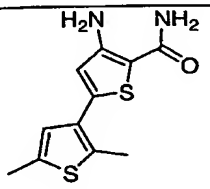


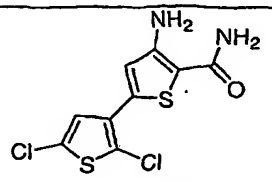
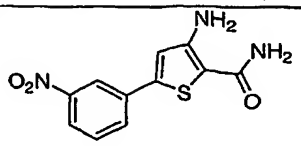
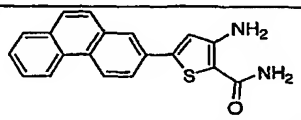
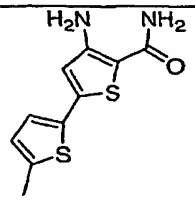
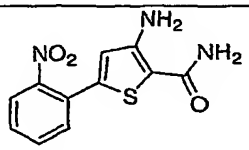
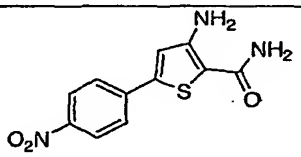
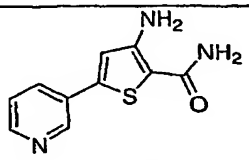
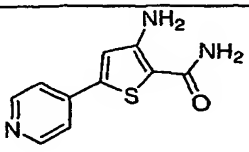
3-Aminobenzo[b]thiophene-2-carboxamide

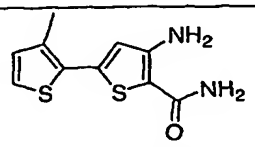
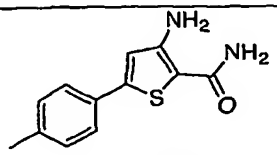
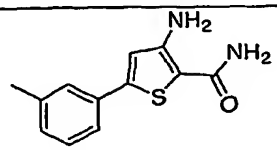
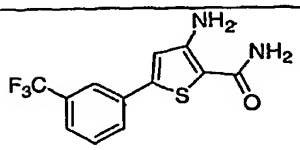
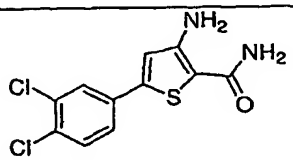
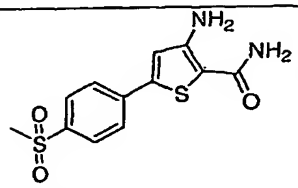
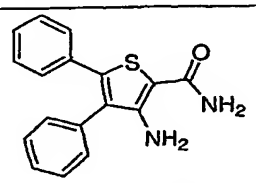
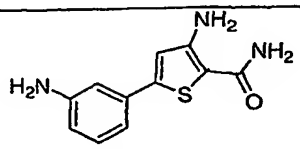
The title compound was prepared using the procedures found in example 33. Steps 1 and 2: ^{1}Hnmr (DMSO (300 MHz) 8.02 (d, 1H, J = 7.65 Hz); 7.82 (d, 1H, J = 7.85 Hz); 7.49-7.35 (m 2H); 7.05 (s, 2H).ESHRMS (m/z) 193.0347 (M+H $C_9H_8N_2OS$ requires 193.0346).

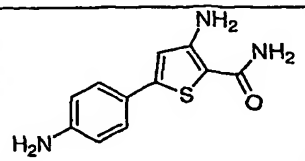
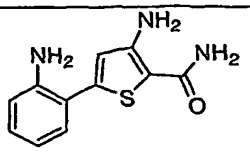
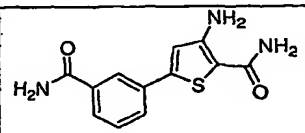
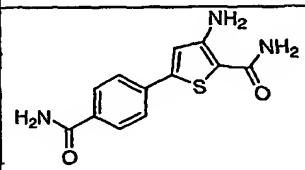
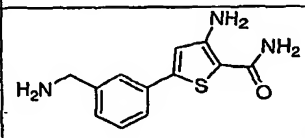
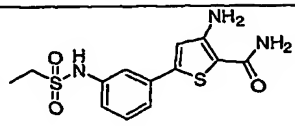
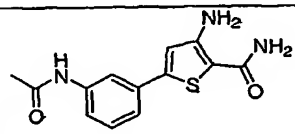
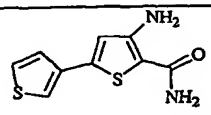
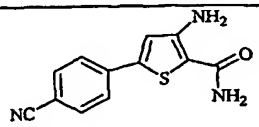
Table 1 shows the bioactivity of exemplified compounds in the heterodimer assay expressed as IC_{50}.

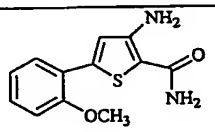
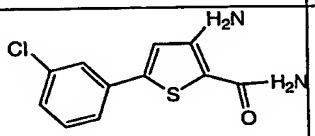
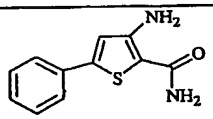
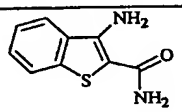
TABLE 1

Example #	Compound	Structure	IC_{50}
Example 1	3-amino-5-(3-methoxyphenyl)thiophene-2-carboxamide		1 ≤ 10 μM
Example 2	3-amino-5-(2-chlorophenyl)thiophene-2-carboxamide		10 ≤ 100 μM
Example 3	3-amino-5-(3-cyanophenyl)thiophene-2-carboxamide		1 ≤ 10 μM
Example 4	4-amino-5'-chloro-2,2'-bithiophene-5-carboxamide		1 ≤ 10 μM
Example 5	4-amino-2',5'-dimethyl-2,3'-bithiophene-5-carboxamide		1 ≤ 10 μM

Example #	Compound	Structure	IC_{50}
Example 6	4-amino-2',5'-dichloro-2,3'-bithiophene-5-carboxamide		10 ≤ 100 μM
Example 7	3-amino-5-(3-nitrophenyl)thiophene-2-carboxamide		1 ≤ 10 μM
Example 8	3-amino-5-(2-phenanthryl)thiophene-2-carboxamide		>100 μM
Example 9	4-amino-5'-methyl-2,2'-bithiophene-5-carboxamide		10 ≤ 100 μM
Example 10	3-amino-5-(2-nitrophenyl)thiophene-2-carboxamide		10 ≤ 100 μM
Example 11	3-amino-5-(4-nitrophenyl)thiophene-2-carboxamide		>100 μM
Example 12	3-amino-5-pyridin-3-ylthiophene-2-carboxamide		10 ≤ 100 μM
Example 13	3-amino-5-pyridin-4-ylthiophene-2-carboxamide		10 ≤ 100 μM

Example #	Compound	Structure	IC_{50}
Example 14	4-amino-3'-methyl-2,2'-bithiophene-5-carboxamide		10 ≤ 100 μM
Example 15	3-amino-5-(4-methylphenyl)thiophene-2-carboxamide		>100 μM
Example 16	3-amino-5-(3-methylphenyl)thiophene-2-carboxamide		>100 μM
Example 17	3-amino-5-[3-(trifluoromethyl)phenyl]thiophene-2-carboxamide		>100 μM
Example 18	3-amino-5-(3,4-dichlorophenyl)thiophene-2-carboxamide		>100 μM
Example 19	3-amino-5-[4-(methylsulfonyl)phenyl]thiophene-2-carboxamide		10 ≤ 100 μM
Example 20	3-amino-4,5-diphenylthiophene-2-carboxamide		>100 μM
Example 21	3-amino-5-(3-aminophenyl)thiophene-2-carboxamide		1 ≤ 10 μM

Example #	Compound	Structure	IC_{50}
Example 22	3-amino-5-(4-aminophenyl)thiophene-2-carboxamide		>100μM
Example 23	3-amino-5-(2-aminophenyl)thiophene-2-carboxamide		>100μM
Example 24	3-amino-5-[3-(aminocarbonyl)phenyl]thiophene-2-carboxamide		10 ≤ 100 μM
Example 25	3-amino-5-[4-(aminocarbonyl)phenyl]thiophene-2-carboxamide		>100 μM
Example 26	3-amino-5-[3-(aminomethyl)phenyl]thiophene-2-carboxamide		10 ≤ 100 μM
Example 27	3-amino-5-{3-[(ethylsulfonyl)amino]phenyl}thiophene-2-carboxamide		10 ≤ 100 μM
Example 28	5-[3-(acetylamino)phenyl]-3-aminothiophene-2-carboxamide		10 ≤ 100 μM
Example 29	3-amino-5-(3-thienyl)thiophene-2-carboxamide		1 ≤ 10 μM
Example 30	3-amino-5-(4-cyanophenyl)thiophene-2-carboxamide		>100μM

Example #	Compound	Structure	IC_{50}
Example 31	3-amino-5-(2-anisyl)-thiophene-2-carboxamide		10 ≤ 100 μM
Example 32	3-amino-5-(3-chlorophenyl)thiophene-2-carboxamide		1 ≤ 10 μM
Example 33	3-Amino-5-phenyl thiophene-2-carboxamide		10 ≤ 100 μM
Example 34	3-Aminobenzo[b]thiophene-2-carboxamide		10 ≤ 100 μM

BIOLOGICAL EVALUATION

[0077] *Materials*

SAM^{2} ™ 96 Biotin capture plates were from Promega. Anti-FLAG affinity resin, FLAG-peptide, NP-40 (Nonidet P-40), BSA, ATP, ADP, AMP, LPS (*E. coli* serotype 0111:B4), and dithiothreitol were obtained from Sigma Chemicals. Antibodies specific for NEMO (IKKγ) (FL-419), IKK1(H-744), IKK2(H-470) and IκBα(C–21) were purchased from Santa Cruz Biotechnology. Ni-NTA resin was purchased from Qiagen. Peptides were purchased from American Peptide Company. Protease inhibitor cocktail tablets were from Boehringer Mannheim. Sephacryl S-300 column was from Pharmacia LKB Biotechnology. Centriprep-10 concentrators with a molecular weight cutoff of 10 kDa and membranes with molecular weight cut-off of 30 kDa were obtained from Amicon. [γ-^{33}P] ATP (2500 Ci/mmol) and [γ-^{32}P] ATP (6000 Ci/mmol) were

purchased from Amersham. The other reagents used were of the highest grade commercially available.

[0078] *Cloning and Expression*

cDNAs of human IKK1 and IKK2 were amplified by reverse transcriptase-polymerase chain reaction from human placental RNA (Clonetech). hIKK1 was subcloned into pFastBac HTa (Life Technologies) and expressed as N-terminal His_6-tagged fusion protein. The hIKK2 cDNA was amplified using a reverse oligonucleotide primer which incorporated the peptide sequence for a FLAG-epitope tag at the C-terminus of the IKK2 coding region (DYKDDDDKD). The hIKK2:FLAG cDNA was subcloned into the baculovirus vector pFastBac. The rhIKK2 (S177S, E177E) mutant was constructed in the same vector used for wild type rhIKK2 using a QuikChange™ mutagenesis kit (Stratagene). Viral stocks of each construct were used to infect insect cells grown in 40L suspension culture. The cells were lysed at a time that maximal expression and rhIKK activity were demonstrated. Cell lysates were stored at -80 °C until purification of the recombinant proteins was undertaken as described below.

[0079] *Enzyme Isolation*

All purification procedures were carried out at 4 °C unless otherwise noted. Buffers used are: buffer A: 20 mM Tris-HCl, pH 7.6, containing 50 mM NaCl, 20 mM NaF, 20 mM β-Glycerophosphate, 500 uM sodiumortho-vanadate, 2.5 mM metabisulfite, 5 mM benzamidine, 1 mM EDTA, 0.5 mM EGTA, 10% glycerol, 1 mM DTT, 1X Complete™ protease inhibitors; buffer B: same as buffer A, except 150 mM NaCl, and buffer C: same as buffer A, except 500 mM NaCl.

[0080] *Isolation of rhIKK1 homodimer*

Cells from an 8 liter fermentation of baculovirus-expressed IKK1 tagged with His peptide were centrifuged and the cell pellet (MOI 0.1, I=72 hr) was re-suspended in 100 ml of buffer C. The cells were microfluidized and centrifuged at 100,000 X g for 45 min. The supernatant was collected, imidazole added to the final concentration of 10 mM and incubated with 25 ml of Ni-NTA resin for 2 hrs. The suspension was poured into a 25 ml column and washed with 250 ml of buffer C and then with 125 ml of 50 mM imidazole in buffer C. rhIKK1 homodimer was eluted using 300 mM imidazole in buffer C. BSA and NP-40 were added to the enzyme fractions to the final concentration of 0.1 %. The enzyme was dialyzed against buffer B, aliquoted and stored at -80 °C.

[0081] ***Isolation of rhIKK2 homodimer***

A 10 liter culture of baculovirus-expressing IKK2 tagged with FLAG peptide was centrifuged and the cell pellet (MOI=0.1 and I=72 hrs) was re-suspended in buffer A. These cells were microfluidized, and centrifuged at 100,000 X g for 45 min. Supernatant was passed over a G-25 column equilibrated with Buffer A. Protein peak was collected and incubated with anti-FLAG affinity resin on a rotator overnight in buffer B. The resin was washed in batch with 10-15 bed volumes of buffer C. Washed resin was poured into a column and rhIKK2 homodimer was eluted using 5 bed volumes of buffer B containing FLAG peptide. 5 mM DTT, 0.1% NP-40 and BSA (concentrated to 0.1% in final amount) was added to the eluted enzyme before concentrating in using an Amicon membrane with a molecular weight cut-off of 30 kDa. Enzyme was aliquoted and stored at -80 °C.

[0082] ***Isolation of rhIKK1/IKK2 heterodimer***

The heterodimer enzyme was produced by coinfection in a baculovirus system (FLAG IKK2/IKK1 His; MOI=0.1 and I=72 hrs). Infected cells were centrifuged and the cell pellet (10.0 g) was suspended in 50 ml of buffer A. The protein suspension was microfluidized and centrifuged at 100,000 X g for 45

min. Imidazole was added to the supernatant to a final concentration of 10 mM. The protein was allowed to bind 25 ml of Ni-NTA resin by mixing for 2 hrs. The protein-resin slurry was poured into a 25 ml column and washed with 250 ml of buffer A containing 10 mM imidazole followed by 125 ml of buffer A containing 50 mM imidazole. Buffer A, containing 300 mM imidazole, was then used to elute the protein. A 75 ml pool was collected and NP-40 was added to a final concentration of 0.1%. The protein solution was then dialyzed against buffer B. The dialyzed heterodimer enzyme was then allowed to bind to 25 ml of anti-FLAG M2 agarose affinity gel overnight with constant mixing. The protein-resin slurry was then centrifuged for 5 min at 2,000 rpm. The supernatant was collected and the resin re-suspended in 100 ml of buffer C containing 0.1% NP-40. The resin was washed with 375 ml of buffer C containing 0.1 % NP-40. The protein-resin was poured into a 25 ml column and the enzyme eluted using buffer B containing FLAG peptide. Enzyme fractions (100 ml) were collected and concentrated to 20 ml using an Amicon membrane with molecular weight cut-off of 30 kDa. Bovine serum albumin was added to the concentrated enzyme to final concentration of 0.1 %. The enzyme was then aliquoted and stored at -80 °C.

[0083] *Cell Culture*

The wild type (wt) human pre-B cell line, 70Z/3, and its mutant, 1.3E2, were generously provided by Dr. Carol Sibley. Wt 70Z/3 and 1.3E2 cells were grown in RPMI 1640 (Gibco) supplemented with 7 % defined bovine serum (Hyclone) and 50 μM 2-mercaptoethanol. Human monocytic leukemia THP-1 cells, obtained from ATCC, were cultured in RPMI 1640 supplemented with 10% defined bovine serum, 10 mM HEPES, 1.0 mM sodium pyruvate and 50 μM 2-mercaptoethanol. For experiments, cells were plated in 6 well plates at $1x10^6$ cells/ml in fresh media. Pre-B cells were stimulated by the addition of 10 μg/ml LPS for varying lengths of time ranging from 0-4 hr. THP-1 cells were stimulated by the addition of 1 μg/ml LPS for 45 minutes. Cells were pelleted, washed with cold 50 mM sodium phosphate buffer, pH 7.4 containing 0.15 M

NaCl and lysed at 4 °C in 20 mM Hepes buffer, pH 7.6 containing 50 mM NaCl, 1 mM EDTA, 1 mM EGTA, 1 mM sodium orthovanadate, 10 mM β-glycerophosphate, 1 mM NaF, 1 mM PMSF, 1 mM DTT and 0.5 % NP40 (lysis buffer). The cytosolic fractions obtained following centrifugation at 10,000 X g were stored at -80° C until used.

[0084] ***Immunoprecipitation and Western Blotting***

SF9 cells paste containing rhIKKs were centrifuged (100,000 X g, 10 min) to remove debris. rhIKKs were immunoprecipitated (100 μg of cell paste) from the cell supernatant using 3 μg of anti-NEMO antibody (FL-419), followed by coupling to protein A sepharose beads. rhIKKs were also immunoprecipitated from affinity chromatography purified protein preparations (1 μg) using anti-FLAG, anti-His or anti-NEMO antibodies (1-4 μg) followed by protein A sepharose coupling. The native, human IKK complex was immunoprecipitated from THP-1 cell homogenates (300 μg/condition) using the anti-NEMO antibody. Immune complexes were pelleted and washed 3 times with 1 ml cold lysis buffer. Immunoprecipitated rhIKKs were chromatographed by SDS-PAGE (8% Tris-glycine) and transferred to nitrocellulose membranes (Novex) and detected by chemiluminescense (SuperSignal) using specific anti-IKK antibodies (IKK2 H-470, IKK1 H-744). Native IKK2, IκBα and NEMO proteins from cytosolic lysates (20-80 μg) were separated by SDS-PAGE and visualized by chemiluminescense using specific antibodies.

[0085] ***Phosphatase Treatment***

Immunoprecipitated rhIKKs were washed 2 times in 50 mM Tris-HCl, pH 8.2 containing 0.1 mM EDTA, 1 mM DTT, 1 mM PMSF and 2 mM $MnCl_2$ and resuspended in 50 μl. Phosphatase (λPPase, 1000 U) was pre-diluted in the same buffer and added to the IKK samples. Following an incubation at room temperature for 30 minutes with intermittent mixing, cold lysis buffer was

added to the tubes to stop the reaction. After several washes, 10 % of the beads were removed for Western analysis, and the remaining material was pelleted and resuspended in 100 µl of the buffer used for the *in vitro* kinase assay.

[0086] ***IKKα SAM Enzyme Assay***

IKKα kinase activity was measured using a biotinylated IκBα peptide (Gly-Leu-Lys-Lys-Glu-Arg-Leu-Leu-Asp-Asp-Arg-His-Asp-Ser_{32}-Gly-Leu-Asp-Ser_{36}-Met-Lys-Asp-Glu-Glu), a SAM^2 ™ 96 Biotin capture plate, and a vacuum system. The standard reaction mixture contained 5 µM biotinylated IκBα peptide, 1 µM [γ-^{33}P] ATP (about 1 X 10^5 cpm), 1 mM DTT, 50 mM KCl, 2 mM $MgCl_2$, 2 mM $MnCl_2$, 10 mM NaF, 25 mM Hepes buffer, pH. 7.6 and enzyme solution (1-10 µl) in a final volume of 50 µl. After incubation at 25 °C for 30 min, 25 µl of the reaction mixture was withdrawn and added to a SAM^2 ™ 96 Biotin capture 96-well plate. Each well was then washed successively with 800 µl 2 M NaCl, 1.2 ml of NaCl containing 1% H_3PO_4, 400 µl H_2O, and 200 µl 95% ethanol. The plate was allowed to dry in a hood at 25 °C for 1 hr and then 25 µl of scintillation fluid (Microscint 20) was added to each well. Incorporation of [γ-^{33}P] ATP was measured using a Top-Count NXT (Packard). Under each assay condition, the degree of phosphorylation of IκBα peptide substrate was linear with time and concentration for all purified enzymes. Results from the biotinylated peptide assay were confirmed by SDS-PAGE analysis of kinase reaction utilizing a GST-IκBα$_{1-54}$ and [γ-^{32}P] ATP. The resulting radiolabeled substrate was quantitated by Phosphoimager (Molecular Dynamics). An ion exchange resin assay was also employed using [γ-^{33}P] ATP and GST-IκBα$_{1-54}$ fusion protein as the substrates. Each assay system yielded consistent results in regard to K_m and specific activities for each of the purified kinase isoforms. One unit of enzyme activity was defined as the amount required to catalyze the transfer of 1 nmole of phosphate from ATP to IκBα peptide per min. Specific activity was expressed as units per mg of protein. For experiments related to K_m determination of purified enzymes, various

concentrations of ATP or IκBα peptide were used in the assay at either a fixed IκBα or ATP concentration. For IκBα peptide K_m, assays were carried out with 0.1 μg of enzyme, 5 μM ATP and IκBα peptide from 0.5 to 20 μM. For ATP K_m, assays were carried out with 0.1 μg of enzyme, 10 μM IκBα peptide and ATP from 0.1 to 10 μM. For K_m determination of rhIKK1 homodimer, due to its low activity and higher K_m for IκBα peptide, rhIKK1 homodimer (0.3 μg) was assayed with 125 μM IκBα peptide and a 5-fold higher specific activity of ATP (from 0.1 to 10 μM) for ATP K_m experiments and a 5-fold higher specific activity of 5 μM ATP and IκBα peptide (from 5 to 200 μM) for IκBα peptide K_m experiments.

[0087] ***IKKβ Resin Enzyme Assay***

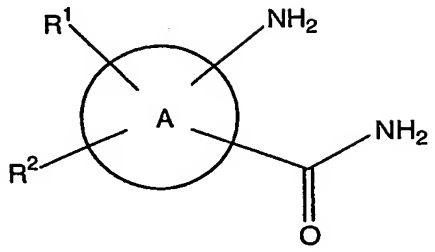
IKKβ kinase activity was measured using a biotinylated IκBα peptide (Gly-Leu-Lys-Lys-Glu-Arg-Leu-Leu-Asp-Asp-Arg-His-Asp-Ser_{32}-Gly-Leu-Asp-Ser_{36}-Met-Lys-Asp-Glu-Glu) (American Peptide Co.). 20 ul of the standard reaction mixture contained 5 μM biotinylated IκBα peptide, 0.1 μCi/reaction [γ-^{33}P] ATP (Amersham) (about 1 X 10^5 cpm), 1 μM ATP (Sigma), 1 mM DTT (Sigma), 2 mM $MgCl_2$ (Sigma), 2 mM $MnCl_2$ (Sigma), 10 mM NaF (Sigma), 25 mM Hepes (Sigma) buffer, pH 7.6 and 20 μl enzyme solution and 10 ul inhibitor in a final volume of 50 μl. After incubation at 25 °C for 30 min, 150 μl resin (Dowex anion-exchange resin AG1X8 200-400 mesh) in 900 mM formate, pH 3.0 was added to each well to stop the reaction. Resin was allowed to settle for one hour and 50 ul of supernatant was removed to a Micolite-2 flat bottom plate (Dynex). 150 μl of scintillation fluid (Microscint 40) (Packard) was added to each well. Incorporation of [γ-^{33}P] ATP was measured using a Top-Count NXT (Packard).

[0088] ***IKK heterodimer Resin Enzyme Assay***

IKK heterodimer kinase activity was measured using a biotinylated IκBα peptide (Gly-Leu-Lys-Lys-Glu-Arg-Leu-Leu-Asp-Asp-Arg-His-Asp-Ser_{32}-Gly-Leu-Asp-Ser_{36}-Met-Lys-Asp-Glu-Glu) (American Peptide Co.). 20 ul of the standard reaction mixture contained 5 μM biotinylated IκBα peptide, 0.1 μCi/reaction [γ-^{33}P] ATP (Amersham) (about 1 X 10^5 cpm), 1 μM ATP (Sigma), 1 mM DTT (Sigma), 2 mM $MgCl_2$ (Sigma), 2 mM $MnCl_2$ (Sigma), 10 mM NaF (Sigma), 25 mM Hepes (Sigma) buffer, pH 7.6 and 20 μl enzyme solution and 10 μl inhibitor in a final volume of 50 μl. After incubation at 25 °C for 30 min, 150 μl resin (Dowex anion-exchange resin AG1X8 200-400 mesh) in 900 mM formate, pH 3.0 was added to each well to stop the reaction. Resin was allowed to settle for one hour and 50 ul of supernatant was removed to a Micolite-2 flat bottom plate (Dynex). 150 μl of scintillation fluid (Microscint 40) (Packard) was added to each well. Incorporation of [γ-^{33}P] ATP was measured using a Top-Count NXT (Packard).

WHAT IS CLAIMED IS:

1. A compound of formula I



wherein

A is a 5-membered heteroaromatic ring containing one or two heteroatoms independently selected from oxygen, nitrogen, or sulfur;

R^1 is selected from the group consisting of: hydrogen, halogen, cyano, nitro, $-N(R^3)_2$, $-CON(R^3)_2$, $-COOR^3$, $-NR^3COR^3$, $S(O)_mR^3$, $-SO_2N(R^3)_2$, $-NR^3SO_2R^3$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, substituted or unsubstituted aryl, and a substituted or unsubstituted 5- to 7-membered heteroaromatic ring containing one to three heteroatoms independently selected from oxygen, nitrogen, or sulfur, wherein said substituent(s) are independently selected from the group consisting of: halogen, cyano, nitro, $-N(R^4)_2$, $-CON(R^4)_2$, $-COOR^4$, $-NR^4COR^4$, $S(O)_mR^4$, $-SO_2N(R^4)_2$, $-NR^4SO_2R^4$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, aminoalkyl, and aryl;

R^2 is selected from the group consisting of: substituted or unsubstituted aryl, and a 5- to 7-membered substituted or unsubstituted heteroaromatic ring containing one to three

heteroatoms independently selected from oxygen, nitrogen, or sulfur, wherein said substituent(s) are independently selected from the group consisting of: halogen, cyano, nitro, $-N(R^4)_2$, $-CON(R^4)_2$, $-COOR^4$, $-NR^4COR^4$, $S(O)_mR^4$, $-SO_2N(R^4)_2$, $-NR^4SO_2R^4$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, aminoalkyl, and aryl;

R^1 and R^2 can optionally be taken together form a 5 or 6 membered saturated or unsaturated ring optionally substituted with one or more substituent selected from the group consisting of: halogen, cyano, nitro, $-N(R^3)_2$, $-CON(R^3)_2$, $-COOR^3$, $-NR^3COR^3$, $S(O)_mR^3$, $-SO_2N(R^3)_2$, $-NR^3SO_2R^3$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, substituted or unsubstituted aryl, and a substituted or unsubstituted 5- to 7-membered heteroaromatic ring containing one to three heteroatoms independently selected from oxygen, nitrogen, or sulfur, wherein said substituent(s) are independently selected from the group consisting of: halogen, cyano, nitro, $-N(R^4)_2$, $-CON(R^4)_2$, $-COOR^4$, $-NR^4COR^4$, $S(O)_mR^4$, $-SO_2N(R^4)_2$, $-NR^4SO_2R^4$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, aminoalkyl, and aryl;

R^3 is selected from the group consisting of: hydrogen or alkyl;

R^4 is selected from the group consisting of: hydrogen or alkyl;

m is an integer 0, 1, or 2; and

isomers, tautomers, carriers, prodrugs, pharmaceutically acceptable salts thereof.

2. The compound of claim 1

wherein

R^1 is hydrogen; and

R^2 is selected from the group consisting of: substituted or unsubstituted aryl, and a 5- to 7-membered substituted or unsubstituted heteroaromatic ring containing one to three heteroatoms independently selected from oxygen, nitrogen, or sulfur, wherein said substituent(s) are independently selected from the group consisting of: halogen, cyano, nitro, $-N(R^4)_2$, $-CON(R^4)_2$, $-COOR^4$, $-NR^4COR^4$, $S(O)_mR^4$, $-SO_2N(R^4)_2$, $-NR^4SO_2R^4$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, aminoalkyl, and aryl;

3. The compound of claim 1

wherein

R^1 and R^2 taken together form a 5 or 6 membered saturated or unsaturated ring optionally substituted with one or more substituent selected from the group consisting of: halogen, cyano, nitro, $-N(R^3)_2$, $-CON(R^3)_2$, $-COOR^3$, $-NR^3COR^3$, $S(O)_mR^3$, $-SO_2N(R^3)_2$, $-NR^3SO_2R^3$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, substituted or unsubstituted aryl, and a substituted or unsubstituted 5- to 7-membered heteroaromatic ring containing one to three heteroatoms independently selected from oxygen, nitrogen, or sulfur, wherein said substituent(s) are independently selected from the group consisting of: halogen, cyano, nitro, $-N(R^4)_2$, $-CON(R^4)_2$, $-COOR^4$, $-NR^4COR^4$, $S(O)_mR^4$, $-SO_2N(R^4)_2$, $-NR^4SO_2R^4$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, aminoalkyl, and aryl;

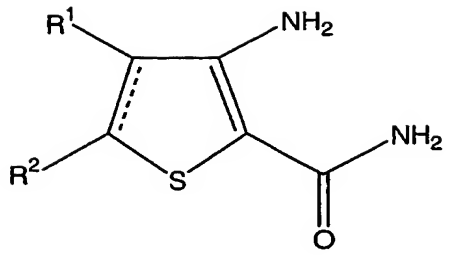
4. The compound of claim 1

wherein

R^1 is selected from the group consisting of: hydrogen, halogen, cyano, nitro, $-N(R^3)_2$, $-CON(R^3)_2$, $-COOR^3$, $-NR^3COR^3$, $S(O)_mR^3$, $-SO_2N(R^3)_2$, $-NR^3SO_2R^3$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, substituted or unsubstituted aryl, and a substituted or unsubstituted 5- to 7-membered heteroaromatic ring containing one to three heteroatoms independently selected from oxygen, nitrogen, or sulfur, wherein said substituent(s) are independently selected from the group consisting of: halogen, cyano, nitro, $-N(R^4)_2$, $-CON(R^4)_2$, $-COOR^4$, $-NR^4COR^4$, $S(O)_mR^4$, $-SO_2N(R^4)_2$, $-NR^4SO_2R^4$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, aminoalkyl, and aryl; and

R^2 is selected from the group consisting of: substituted or unsubstituted aryl, and a 5- to 7-membered substituted or unsubstituted heteroaromatic ring containing one to three heteroatoms independently selected from oxygen, nitrogen, or sulfur, wherein said substituent(s) are independently selected from the group consisting of: halogen, cyano, nitro, $-N(R^4)_2$, $-CON(R^4)_2$, $-COOR^4$, $-NR^4COR^4$, $S(O)_mR^4$, $-SO_2N(R^4)_2$, $-NR^4SO_2R^4$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, aminoalkyl, and aryl.

5. A compound of the formula II



R^1 is selected from the group consisting of: hydrogen, halogen, cyano, nitro, $-N(R^3)_2$, $-CON(R^3)_2$, $-COOR^3$, $-NR^3COR^3$, $S(O)_mR^3$, $-SO_2N(R^3)_2$, $-NR^3SO_2R^3$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, substituted or unsubstituted aryl, and a substituted or unsubstituted 5- to 7-membered heteroaromatic ring containing one to three heteroatoms independently selected from oxygen, nitrogen, or sulfur, wherein said substituent(s) are independently selected from the group consisting of: halogen, cyano, nitro, $-N(R^4)_2$, $-CON(R^4)_2$, $-COOR^4$, $-NR^4COR^4$, $S(O)_mR^4$, $-SO_2N(R^4)_2$, $-NR^4SO_2R^4$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, aminoalkyl, and aryl;

R^2 is selected from the group consisting of: substituted or unsubstituted aryl, and a 5- to 7-membered substituted or unsubstituted heteroaromatic ring containing one to three heteroatoms independently selected from oxygen, nitrogen, or sulfur, wherein said substituent(s) are independently selected from the group consisting of: halogen, cyano, nitro, $-N(R^4)_2$, $-CON(R^4)_2$, $-COOR^4$, $-NR^4COR^4$, $S(O)_mR^4$, $-SO_2N(R^4)_2$, $-NR^4SO_2R^4$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, aminoalkyl, and aryl;

R^1 and R^2 can optionally be taken together form a 5 or 6 membered saturated or unsaturated ring optionally substituted with one or more substituent selected from the group consisting

of: halogen, cyano, nitro, $-N(R^3)_2$, $-CON(R^3)_2$, $-COOR^3$, $-NR^3COR^3$, $S(O)_mR^3$, $-SO_2N(R^3)_2$, $-NR^3SO_2R^3$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, substituted or unsubstituted aryl, and a substituted or unsubstituted 5- to 7-membered heteroaromatic ring containing one to three heteroatoms independently selected from oxygen, nitrogen, or sulfur, wherein said substituent(s) are independently selected from the group consisting of: halogen, cyano, nitro, $-N(R^4)_2$, $-CON(R^4)_2$, $-COOR^4$, $-NR^4COR^4$, $S(O)_mR^4$, $-SO_2N(R^4)_2$, $-NR^4SO_2R^4$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, aminoalkyl, and aryl;

R^3 is selected from the group consisting of: hydrogen or alkyl;

R^4 is selected from the group consisting of: hydrogen or alkyl;

m is an integer 0, 1, or 2; and

isomers, tautomers, carriers, prodrugs, pharmaceutically acceptable salts thereof.

6. The compound of claim 5

wherein

R^1 is hydrogen; and

R^2 is selected from the group consisting of: substituted or unsubstituted aryl, and a 5- to 7-membered substituted or unsubstituted heteroaromatic ring containing one to three heteroatoms independently selected from oxygen, nitrogen, or sulfur, wherein said substituent(s) are independently selected

from the group consisting of: halogen, cyano, nitro, $-N(R^4)_2$, $-CON(R^4)_2$, $-COOR^4$, $-NR^4COR^4$, $S(O)_mR^4$, $-SO_2N(R^4)_2$, $-NR^4SO_2R^4$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, aminoalkyl, and aryl.

7. The compound of claim 5 wherein

R^1 and R^2 taken together form a 5 or 6 membered saturated or unsaturated ring optionally substituted with one or more substituent selected from the group consisting of: halogen, cyano, nitro, $-N(R^3)_2$, $-CON(R^3)_2$, $-COOR^3$, $-NR^3COR^3$, $S(O)_mR^3$, $-SO_2N(R^3)_2$, $-NR^3SO_2R^3$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, substituted or unsubstituted aryl, and a substituted or unsubstituted 5- to 7-membered heteroaromatic ring containing one to three heteroatoms independently selected from oxygen, nitrogen, or sulfur, wherein said substituent(s) are independently selected from the group consisting of: halogen, cyano, nitro, $-N(R^4)_2$, $-CON(R^4)_2$, $-COOR^4$, $-NR^4COR^4$, $S(O)_mR^4$, $-SO_2N(R^4)_2$, $-NR^4SO_2R^4$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, aminoalkyl, and aryl.

8. The compound of claim 5 wherein

R^1 is selected from the group consisting of: hydrogen, halogen, cyano, nitro, $-N(R^3)_2$, $-CON(R^3)_2$, $-COOR^3$, $-NR^3COR^3$, $S(O)_mR^3$, $-SO_2N(R^3)_2$, $-NR^3SO_2R^3$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, substituted or unsubstituted aryl, and a substituted or unsubstituted 5- to 7-membered heteroaromatic ring containing one to three heteroatoms independently selected from oxygen, nitrogen, or sulfur, wherein said substituent(s) are independently selected

from the group consisting of: halogen, cyano, nitro, $-N(R^4)_2$, $-CON(R^4)_2$, $-COOR^4$, $-NR^4COR^4$, $S(O)_mR^4$, $-SO_2N(R^4)_2$, $-NR^4SO_2R^4$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, aminoalkyl, and aryl; and

R^2 is selected from the group consisting of: substituted or unsubstituted aryl, and a 5- to 7-membered substituted or unsubstituted heteroaromatic ring containing one to three heteroatoms independently selected from oxygen, nitrogen, or sulfur, wherein said substituent(s) are independently selected from the group consisting of: halogen, cyano, nitro, $-N(R^4)_2$, $-CON(R^4)_2$, $-COOR^4$, $-NR^4COR^4$, $S(O)_mR^4$, $-SO_2N(R^4)_2$, $-NR^4SO_2R^4$, alkyl, trifluoromethyl, trifluoromethoxy, alkenyl, alkynyl, alkoxy, alkanoyl, aminoalkyl, and aryl.

9. The compound of claim 5 selected from the group consisting of:

3-amino-5-(3-methoxyphenyl)thiophene-2-carboxamide,
3-amino-5-(2-chlorophenyl)thiophene-2-carboxamide,
3-amino-5-(3-cyanophenyl)thiophene-2-carboxamide,
4-amino-5'-chloro-2,2'-bithiophene-5-carboxamide,
4-amino-2',5'-dimethyl-2,3'-bithiophene-5-carboxamide,
4-amino-2',5'-dichloro-2,3'-bithiophene-5-carboxamide,
3-amino-5-(3-nitrophenyl)thiophene-2-carboxamide,
3-amino-5-(2-phenanthryl)thiophene-2-carboxamide,
4-amino-5'-methyl-2,2'-bithiophene-5-carboxamide,
3-amino-5-(2-nitrophenyl)thiophene-2-carboxamide,
3-amino-5-(4-nitrophenyl)thiophene-2-carboxamide,
3-amino-5-pyridin-3-ylthiophene-2-carboxamide,
3-amino-5-pyridin-4-ylthiophene-2-carboxamide,
4-amino-3'-methyl-2,2'-bithiophene-5-carboxamide,
3-amino-5-(4-methylphenyl)thiophene-2-carboxamide,

3-amino-5-(3-methylphenyl)thiophene-2-carboxamide,
3-amino-5-[3-(trifluoromethyl)phenyl]thiophene-2-carboxamide,
3-amino-5-(3,4-dichlorophenyl)thiophene-2-carboxamide,
3-amino-5-[4-(methylsulfonyl)phenyl]thiophene-2-carboxamide,
3-amino-4,5-diphenylthiophene-2-carboxamide,
3-amino-5-(3-aminophenyl)thiophene-2-carboxamide,
3-amino-5-(4-aminophenyl)thiophene-2-carboxamide,
3-amino-5-(2-aminophenyl)thiophene-2-carboxamide,
3-amino-5-[3-(aminocarbonyl)phenyl]thiophene-2-carboxamide,
3-amino-5-[4-(aminocarbonyl)phenyl]thiophene-2-carboxamide,
3-amino-5-[3-(aminomethyl)phenyl]thiophene-2-carboxamide,
3-amino-5-{3-[(ethylsulfonyl)amino]phenyl}thiophene-2-carboxamide,
5-[3-(acetylamino)phenyl]-3-aminothiophene-2-carboxamide,
3-amino-5-(3-thienyl)thiophene-2-carboxamide,
3-amino-5-(4-cyanophenyl)thiophene-2-carboxamide,
3-amino-5-(2-anisyl)-thiophene-2-carboxamide,
3-amino-5-(3-chlorophenyl)-thiophene-2-carboxamide,
3-Amino-5-phenyl thiophene-2-carboxamide, and
3-Aminobenzo[b]thiophene-2-carboxamide.

10. A composition comprising the compound of claim 1, 2, 3, 4, 5, 6, 7, 8, or 9 and at least one pharmaceutically acceptable carrier.

11. A method of treating cancer, inflammation or an inflammation associated disorder in a subject, said method comprising administering to the subject having or susceptible to such cancer, inflammation or inflammation associated disorder, a therapeutically-effective amount of a compound of claim 1, 2, 3, 4, 5, 6, 7, 8, or 9.

12. The method of claim 11 for use in the treatment of cancer.

13. The method of claim 11 for use in the treatment of inflammation.

14. The method of claim 11 for use in the treatment of an inflammation-associated disorder.

15. The method of claim 14 wherein the inflammation-associated disorder is arthritis.

16. The method of claim 14 wherein the inflammation-associated disorder is pain

17. The method of claim 14 wherein the inflammation-associated disorder is fever.

18. A method of inhibiting a protein kinase in a subject, said method comprising administering to the subject having or susceptible to a protein kinase associated disorder, a therapeutically-effective amount of a compound of claim 1, 2, 3, 4, 5, 6, 7, 8, or 9.

19. The method of claim 18 wherein said protein kinase is selected from the group consisting of: protein kinase C in different isoforms, cyclin dependent kinase (cdk), Met, PAK-4, PAK-5, ZC-1, STLK-2, DDR-2, Aurora 1, Aurora 2, Bub-1, PLK, Chk1, Chk2, HER2, raf1, MEK1, MAPK, EGF-R, PDGF-R, FGF-R, IGF-R, VEGF-R, PI3K, weel kinase, Src, Abl, Akt, ILK, MK-2, IKK-2, Cdc7, NekIKK1, IKK2, IKKα/IKKβ heterodimer, TBK and IKK*i*.

20. The method of claim 18 wherein said protein kinase is selected from the group consisting of: IKK2, IKKα/IKKβ heterodimer, TBK and IKK*i*.

21. The method of claim 18 wherein said protein kinase is IKK2.